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ANNALS OF INTERNAL MEDICINE

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*Deceased

On the Milder Affective Disorders

(Sometimes Unrecognized or Misinterpreted by the General Practitioner)*

By Lewellys F. Barker, M.D., *Baltimore*

By affective disorders, I mean pathological disturbances of the feeling-tone, the mood, and the emotional life of patients. There are many varieties of these disorders, but I shall limit my discussion at this time to the milder depressions and the milder elations that are often observable in patients of the so-called cyclothymic or elative-depressive constitution. Though such affective disorders are usually easily recognizable by practitioners who have been trained in neuropsychiatry, they are undoubtedly often overlooked or entirely misunderstood by physicians and surgeons who have had but little experience in the study of abnormal mental states. An outspoken depression or melancholy of severe grade, with delusions of poverty, of unworthiness and of sin and with ideas of, or attempts at, suicide, will scarcely escape recognition, even by the tyro; nor will an exaggerated expansive state with great elation, with delusions of grandeur, with extravagant self-appreciation, with marked push of talk and pressure of activity and with aggressive attacks upon the surroundings be likely to go undiagnosed.

It is very common, however, to find that the milder depressive and expansive states, as well as the mixed states in which symptoms of elation and of depression are combined in the same patient, are wrongly diagnosed; very often the symptoms are attributed to accidentally associated somatic disorders, or to mere neurasthenia or hysteria. A few case-histories, briefly epitomized, will illustrate some of the types of disorder I have in mind better perhaps than longer and more detailed descriptions.

Case I

Second Attack of Depression in Patient Who Attributed Her Symptoms to Somatic Disorder.

Mrs. L., aet. 52. *Complaints*: "nervous" for preceding 10 months; inability to make decisions; loss of interests; tendency to worry; tinnitus; insomnia; anorexia; constipation alternating with diarrhoea, burning in rectum.

She received treatment in several hospitals and sanitaria but without relief of symptoms. She consulted a long series of physicians, as well as a Christian Science healer. She was operated upon for hemorrhoids and rectal fissures; she was treated in one hospital for suspected amebic dysentery, in another for spasm of the colon and mucous colitis associated with abdominal pain. Patient attributed her sufferings partly to fright in an

*Read at the Boston meeting of the American College of Physicians, April 8th, 1929.

automobile accident, partly to her rectal operation.

One friend tried to cure her by taking her on visits to the slums and showing her the intense poverty of people who were even worse off than she thought herself to be. Bromides and luminal have been taken in large quantities for the nervousness and insomnia. Patient has grown greatly discouraged; wishes she could die.

Diagnostic survey revealed, in addition to the affective disorder, some oral sepsis, a mild secondary anemia, a spastic colon, and moderate obesity (20 pounds over ideal weight).

On inquiry it was found that 23 years earlier (at the age of 29) she had passed through an attack of depression accompanied by long periods of weeping from which she gradually recovered without hospitalization.

Case II

Fourth Recurrent Depressive State in Patient of Cyclothymic Constitution.

Mrs. H., aet. 40. *Complaints*: "nervous breakdown; tenseness without power to relax; sensation of drawing in and about eye balls; inability to eat and loss of 50 pounds in weight; insomnia; headaches; weakness; weeping spells; irritation because impossible to rise above her symptoms; difficulty in making decisions; several abdominal operations without relief of symptoms; greatly discouraged."

Diagnostic survey revealed, in addition to the affective disorder, chronic tonsillitis, intestinal stasis, a mild cystitis, slight hyperthyroidism and profound undernutrition (46 pounds below calculated ideal weight).

A study of the earlier history showed that the patient had suffered from three attacks of depression in the preceding sixteen years and that her mother had also been the victim of recurrent depressions.

The patient reports that in her "well periods" she is very active and everyone is astonished at her energy; she entertains a great deal, works hard, engages in a whole series of social, religious and philanthropic activities, and is of a joyous and very happy nature. She cannot understand her present sadness, fatiguability, loss of interests, and feelings of insufficiency.

Case III

Sixth Recurrent Depressive State with Familial History of Depression.

Mrs. T., aet. 46. *Complaints*: "Bad teeth and tonsils; great nervousness; insomnia; weeping spells; constant feelings of physical fatigue and exhaustion; panicky feelings; tenseness; always anxious."

Diagnostic survey revealed, in addition to her affective disorder, severe oral sepsis (eleven infected teeth), chronic constipation and hemorrhoids, uterine myoma, low blood pressure and slight hypothyroidism.

A close analysis of the patient's previous history showed that she had passed through no less than five periods of depression. Each attack had lasted many months. In some of her depressions she harboured definitely suicidal ideas and required sanitarium treatment. In one attack, while under treatment in a hospital for nervous diseases she ran away, returning to her own home "to fight it out by herself." One of her uncles committed suicide while in a period of depression.

Case IV

Expansive Dynamic Personality with Recurrent Depressive "Slumps."

Mr. G., aet. 68, a prominent financier of prodigious energy and activity, returns to the hospital at intervals of a year or two, usually with some somatic complaint (joint pains, sinus troubles, digestive disturbances), but really because of recurrent periods of exhaustion, loss of usual feeling of vigor, let down of interests and mild depression.

Diagnostic surveys, at one or another visit, have revealed, in addition to the affective disorder, oral sepsis, slight paranasal sinusitis, hemorrhoids, moderate obesity, anginoid pains, slight anemia, low blood pressure, benign prostatic hypertrophy, and slight hypertrophic osteoarthritis.

Studies of the life-history of the patient show that he has achieved noteworthy success in the business world, is much beloved

and admired, and has hosts of friends to whom he writes long, jolly letters in a large, bold hand. Except in what he calls his "slumps," he is exceedingly optimistic and happy, shows great pressure of activity, travels much (sometimes 35,000 miles in one year), exhibits "push of talk," writes jingles, and wishes to "stick around the good old world for years to come, enjoying good health and never to become an extinct volcano." In other words, when he is what he calls "well," he has a very dynamic expansive personality, pushes himself far beyond his strength, but gets great satisfaction out of accomplishment. He admits that nobody in the world can control him unless he controls himself. His wife and friends are powerless to stop him in his tremendous physical and mental activity which amounts to a veritable "drive."

His brother once spent several months under my care in a hospital because of an affective disorder in which there was marked loss of interest, fatiguability and depression.

Case V

Mixed State: Predominantly Expansive Psychosis with Depressive Components.

Mrs. O., aet. 56. *Chief Complaints*: "fear of cancer; insomnia; red and watery eyes; sinking spells." She has attacks called "vasomotor crises" in which there is tingling of the fingers, cold extremities, flushing of the face, palpitation of the heart and tachycardia with some rise in blood pressure.

A diagnostic survey revealed, in addition to the neuropsychiatric malady, a slight chronic arthritis, obesity, and a refraction error in the eyes.

The patient maintains that she must rest quietly in bed for fear of precipitating a "vasomotor crisis." Except that she is obese she looks as though she were in blooming health; her eyes are very bright and somewhat watery and she has a high color. She talks volubly of her symptoms, is obviously egocentric, and laughs and jokes much. She writes many rhymes and jingles, which she dedicates to her physicians. The nursing problem has been very difficult; she has had some seven changes of special nurse, in as many weeks of observation. In several instances she has, herself, demanded change of nurse because of "inattention," "failure to carry out orders," or "unfriendliness"; on the other hand, three of the nurses begged to be relieved of the care of the patient because of excessive and sometimes unnecessary demands, her sarcastic remarks and her general attitude that became to them unbearable. All seven of these nurses were regarded as well-trained and had not experienced any difficulty in the nursing of other patients. The nursing problem became so acute that transfer of the patient to a closed institution is contemplated. The patient's son has several times been under treatment in asylums because of maniacal outbreaks.

Recognition of the Depressive States

Negative Feeling Tone.—The affective life in depressed patients is dominated to a greater or less degree by negative feeling tone. The patients complain of discomfort and torture (worse they say than physical pain) and of loss of capacity for pleasure. They are sad, blue, and gloomy. They are pessimistic and see everything through dark coloured spectacles—not only their own lives but also their surroundings. They become greatly discouraged, and complain bitterly of loss of vigor and of normal interests. They feel insufficient for their everyday duties, find it difficult to make decisions, and tend to blame themselves for failure to surmount their difficulties. There is usually a diurnal variation in the symptoms, the patients being more depressed in the earlier parts of the day.

Anxiety.—Many of the patients complain of a vague general anxiety; others localize feelings of anxiety or

oppression in the precordial region, in the head, in the epigastrium or elsewhere. They interpret these anxious feelings as symptoms of some serious or incurable disease or, perhaps, as evidence that they will lose their minds.

Slowing of Thought and Speech and Emergence of Pathological Micromanic Ideas.—In the milder affective disorders there is no clouding of consciousness, no disorientation, and no failure of comprehension. The patients may complain, however, that their thinking is slowed; and they may talk less and more slowly than when they are well. These symptoms help to fix the ideas of inadequacy and of baseness in their minds and to increase the tendencies to self-depreciation and self-blame. Trivial errors or excesses are raked up out of the past and given undue importance as causes of personal or of familial unhappiness. Pathological ideas of unworthiness, of poverty, and of sin may emerge in consciousness and exaggerate the mental torture. The patients assert that they are good for nothing and feel that the condition is humiliating. They say that everything is a burden to them and that they are a burden to others. Often they may become more and more inert and tend to avoid contacts with family, friends, or business associates. In the severer depressions, suicide is always a great danger; even in the milder depressions, the family and the attending physician should always be on the watch both for suicidal ideas and for suicidal impulses.

Deceptive Bodily Symptomatology.—Areas of pain or of paraesthesia may frequently be complained of and may mislead the attending physician. These symptoms may excite the suspicion of angina pectoris, of multiple neuritis, of tabes, of brain tumor, or of serious disorder of the digestive, the circulatory, or the urogenital system.

Recognition of Pathological Expansive States

Domination by Expansive Moods and Emotions.—The affective life in exalted patients is the counterpart of that observable in depressed patients. The feeling-tone is positive rather than negative. The patients appear overhappy and overjoyful, rather than sad. They exhibit "push of talk," laugh and joke on the slightest provocation and often tend to be over-friendly and overactive. They are, however, subject to sudden and often inexplicable changes of mood and not infrequently they show insufficiently motivated irritability, anger, and overaggressiveness toward those about them. Emotional instability is characteristic of them and their euphoric states may suddenly, and without rhyme or reason, give place to episodal states of depression. The expansive patient, as a rule, gives the impression of a preternatural freedom and feeling of well-being; he sees everything through rose-coloured spectacles, is over-optimistic and outspokenly egocentric. He is likely to dress extravagantly and often fantastically. Even in the presence of difficulty and sorrow, he may maintain a holiday mood and so appear unsympathetic and perhaps heartless through failure to manifest, even briefly, consideration for the misfortunes of others.

These patients often exhibit a loss of sense of the value of money and spend it foolishly.

Acceleration of Movement, Thought and Speech; Distractibility; and Emergence of Pathological Grandiose Ideas.—Expansive states are characterized further by pressure of activity, increased ease and rapidity of associations, unusual distractibility, and often by the manifestation of exaggerated ideas of self-importance and power. The patients are often harder to live with than the mildly depressed, for they wear out their families and sometimes also exhaust their few friends.

These patients are prone to be exceedingly alert and over-active; they are over-talkative, restless and must be doing something all the time; everything seems easy for them; and they behave as though they were immune from feelings of fatigue, surprising their companions by their unremittent energy and by their endurance. They often seem vain, are rather over-sure of themselves, and frequently exhibit erotic symptoms. The attention is likely to be superficial and to be easily shifted from one object or idea to another. Their trains of thought suggest the absence of normal inhibitions; they are often incapable of prolonged concentration upon a goal; they tend to be easily distracted, turning their attention very easily from one topic to another; they may thus exhibit a true "flight of ideas." Moreover, they are prone to make puns, to rhyme, to be subject to associations by sound, and to use in close juxtaposition words that begin with the same letter (alliteration).

The elated patient may write a great many letters to friends and acquaintances, often in a very large hand, with excessive spacing of the single enlarged letters, many underlinings, and frequent exclamation points. Indeed, in some patients, the predilection for excessive letter-writing may be more striking than the push of talk. Sometimes, there is marked literary productivity; only recently I have read a novel that made me feel sure that its author must have written it during a period of pathological expansiveness because of the superficiality of the associations, the frequency of alliterative phrases, the abundance of sound associations, and the excess of words and phrases printed in italics.

Bodily Symptoms of Exalted Patients.—Patients who are over-expansive often look as though they were enjoying unusually good health; they appear full-blooded and happy, their eyes are very bright and sometimes watery, they may eat ravenously, and they often give the impression of living much more fully than their fellows. Some of them, however, complain of headaches and of insomnia; moreover, on closer examination, the futility of their performances despite their excessive activity is sometimes easily demonstrable.

Recognition of Mixed Depressive and Expansive States.

Aside from the fact that depressive states and expansive states may be met with in the same patients at different times in their lives, sometimes indeed alternating with considerable regularity (hence the term "cyclothymia"),

it should be borne in mind that many persons exhibit certain depressive symptoms and certain expansive symptoms simultaneously. These mixed states may be particularly puzzling to the physician who has had but little psychiatric training; and among professional psychiatrists there is much difference of opinion as to their proper classification.

Some patients while predominantly depressive also exhibit irritability, querulousness and aggressiveness suggestive of expansive states. Another group with markedly negative feeling-tone may exhibit motor agitation, egocentricity and hypochondriacal traits and because of the latter make insistent claims upon those about them. And a third group of patients obviously depressed may also manifest distractibility and flight of ideas.

On the other hand, one may see a predominantly expansive patient of euphoric mood, who exhibits, associated with this, a certain psychomotor retardation. In a second expansive patient there may be exaggerated self-appreciation and flight of ideas, but along with these symptoms a certain shyness and bashfulness. In still another expansive patient, though the mood may be exalted, there may be no flight of ideas but rather lessened associative activity—the so-called "unproductive elation".

Still other varieties of "mixed states" have been described. The whole matter is still obscure, defying satisfactory attempts at nosological classification. In some of these states we probably have to deal with constitutional alloys of the syntone with the schizoid temperament and of the pyknic with the asthenic habitus.

Conclusions

Among the patients that apply to general practitioners for diagnosis and treatment, many present, in addition to their somatic abnormalities, the problems of affective disorders of lower or higher grade, often overlooked or entirely misunderstood by physicians or surgeons without neuropsychiatric experience. The recognition of such affective disorders and their assignment to their proper nosological positions are of importance for prognosis and for adequate care and treatment. The thorough schooling of medical students in the main facts and principles of modern psychiatry and the more extensive utilization of neuropsychiatric consultants by physicians and surgeons who do general work would seem to be desirable.

In the treatment of the affective disorders, it should be made plain that the depressive phases are circumscribed in time and that they have to "run their course". I like to think, though, that by general hygienic measures we may do something toward shortening the duration of a depression. The patients, except when their disorders are very mild, are best treated away from home, without visits or letters from family or friends, under good nursing care, with close supervision by physicians who understand these disorders, who build up the general health, who protect from forms of therapy that are harmful rather than helpful, and who give all justifiable symptomatic relief until the depression disappears.

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Tuberculosis Theses; Diagnostic, Prognostic, Therapeutic*

By Lawrason Brown, *Saranac Lake, N. Y.*

ARTICLES of faith to which one may subscribe or from which one may dissent are of value in many activities of life. To the beginner in an art they point out a ford across troublous and swift waters. That other easier and safer fords are not to be found or, indeed, do not already exist is not denied but here at least is one. To him who has long practised the art they seem, in part at least, axiomatic and tiresome, or else not to be accepted. Their power to arouse discussion, to lead to thought, to foster healthy disagreement, is all that their author desires. That he will be able to subscribe to them all in some months he doubts, but today they represent what he finds from his experience, colored, no doubt, by that of many others, to serve him as a guide for action.

These theses were published in part some ten or twelve years ago and the author has been surprised to see how extensively he has had to revise and to add to them.

I. Diagnostic Theses.

1. An appearance of ruddy health does not exclude tuberculosis.

2. In any patient with constitutional symptoms, no matter of what he complains, the possibility of tuberculosis must be kept constantly in mind.

3. Prolonged and intimate exposure at any time of life, but especially in childhood, either in home, workshop, or office, is vastly more important in diagnosis than "unassociated" or "non-contact" heredity.

4. When demonstrable pulmonary tuberculosis first develops has never been determined but probably it is nearly always discoverable before the twentieth year.

5. Prolonged contact with tuberculosis may and often does lead to infection, but debilitating conditions are usually necessary to cause this to develop into clinical tuberculosis.

6. Among the debilitating conditions the hyperenthusiastic mode of life, formerly confined to college, now prevalent in high schools, the exposure to cold due to insufficient modern dress and the limitation of the diet during the period of growth, particularly in young girls, play an important part in the development of disease.

7. Constitutional or general symptoms suggest the diagnosis of tuberculosis, while the localizing symptoms point out the organ involved.

8. The history or presence of certain complications, such as fistula-in-

*These theses appeared in part in the American Review of Tuberculosis, 1917, 1; 193-205. Read before the American College of Physicians, April 8, 1929, Boston, Mass. As they now stand they have been revised and augmented.

ano, pleurisy, adenitis, a discharging ear coming on painlessly, are all strongly suggestive of tuberculosis.

9. Pleurisy with effusion, not attributable to other causes, demands a diagnosis of suspected pulmonary tuberculosis and treatment for a time at least.

10. A diagnosis, tentative at least, of pulmonary tuberculosis must be made whenever an individual coughs up a drachm or more of blood that cannot be proved to be due to other causes (e.g., mitral stenosis, etc.)

11. A positive diagnosis of pulmonary must be made whenever hemoptysis of a drachm or more and pleurisy with effusion both occur.

12. Familiarity with a patient lends him no immunity to tuberculosis. Your patients, your friends, your family are as prone to contract and to develop pulmonary tuberculosis as hundreds of others.

13. Symptoms indicate that a patient is sick, while physical signs* point out only the mischief that has been done.

14. Symptoms are a better and more accurate guide to activity than are physical signs.

15. Symptoms without abnormal physical signs demand treatment, while abnormal physical signs without symptoms require often only careful watching.

16. While the temperature and pulse may be normal, slight but persistent rise in temperature and slight increase in rapidity of pulse are often present early in the disease.

17. The "usual" weight of a patient who develops pulmonary tuberculosis is frequently ten pounds below the standard weight for his height and age.

18. Failure to interpret rightly the significance of symptoms, or to detect the presence of abnormal physical signs, can be condoned; but failure to ask for and to examine the sputum repeatedly in any patient with chronic cough is inexcusable.

19. Absence of tubercle bacilli in the sputum suggests only that bronchial ulceration is not present.

20. When diagnosis leans heavily upon the sputum examination at least 3 or 4 typical tubercle bacilli must be found.

21. The importance of the usual negative physical examination in the exclusion of pulmonary tuberculosis has been over emphasized.

22. No single physical sign is pathognomonic of pulmonary tuberculosis.

23. Auscultation and roentgenography are the most important procedures in the detection of abnormal physical findings.

24. Inspection may reveal localized retraction of the chest wall and limitations of the chest movement.

25. The detection of râles by auscultation of the inspiration following cough is the most important stethoscopic procedure in the detection of physical signs of early pulmonary tuberculosis.

26. Localized râles, usually moderately coarse, in the upper third of the chest are exceeded in importance only by tubercle baccilli in the sputum and

*These Include X-ray Findings.

by changes upon the roentgenographic film.

27. Such râles may be due also to a rare type of pneumonia, to a clearing acute bronchitis, or to localized pulmonary edema.

28. Changes in percussion and in the relative length, quality, and intensity of the inspiration and expiration are less helpful and less easy to detect.

29. Kronig's tone planes, Riviére's bands of impairment and Pottenger's muscle spasm, while helpful to some, have not proved of great value to many investigators.

30. Measurements of the vital capacity of the lungs are often, probably usually, of little help though possibly of no harm in patients with early tuberculosis.

31. The importance of any physical sign is greatly increased by its persistence in one definite area.

32. The extent of disease as determined by physical signs is usually less than that revealed by the x-ray film (roentgenogram).

33. Abnormal physical signs in the upper third of one lung should be considered as due to pulmonary tuberculosis until proved not to be, while those at the base should be looked upon as non-tuberculous until definitely proved so.

34. Tubercle bacilli alone determine that a basal lesion is tuberculous.

35. Abnormal physical signs should not be stated to be absent until after a second examination several days later.

36. No pulmonary examination is complete without a study of the x-ray films (roentgenograms.)

37. The slighter the lesion the better must be the roentgenograms.

38. Abnormalities on a single film often fade into a normal picture when viewed stereoscopically. Hence in early diagnosis place your dependence upon good stereoscopic films.

39. When diagnosis rests upon the interpretation of the roentgenogram, the mottling, a sine-qua-non, must be irregularly distributed ("parenchymatous" lesion), as the linear arrangement ("peritruncal" lesion) while occurring in pulmonary tuberculosis is insufficient evidence.

40. The fluoroscope, valuable for the study of movement, both normal and pathologic, and for its aid in the treatment by artificial pneumothorax, fails often to reveal slight lesions plainly evident upon the roentgenogram.

41. The extent of disease as revealed by the film exceeds in the majority of cases the extent inferred from the usual abnormal physical signs.

42. Extensive (moderately or even far advanced) pulmonary tuberculosis may be diagnosed from the roentgenogram while the usual physical signs remain slight or inconclusive.

43. A parenchymatous x-ray lesion is present in 96 to 98% of all cases in which tubercle bacilli occur in the sputum.

44. Tubercle bacilli may occur in the sputum when a parenchymatous lesion cannot be found.

45. In the diagnosis of pulmonary tuberculosis the evidence offered by the film usually greatly outweighs that presented by the usual physical examination but the opposite holds true for

many non-tuberculous pulmonary diseases.

46. The roentgenogram is even more important in the diagnosis of pulmonary tuberculosis in early (infancy, childhood) than in adult life.

47. The presence or absence of a complicating intestinal tuberculosis can be determined with accuracy only by roentgenologic study.

48. In every patient with extensive physical signs and no tubercle bacilli in the sputum, the evidence in favor of the diagnosis of pulmonary tuberculosis should be considered and reconsidered.

49. Laryngeal infiltration or ulceration, limited to one side in any patient with doubtful pulmonary findings, is suggestive evidence of the presence of pulmonary tuberculosis.

50. When sputum is lacking or when tubercle bacilli are absent on repeated examinations, the possibility of the presence of bronchiectasis, sinusitis, chronic pulmonary infection, hyperthyroidism, syphilis, endocarditis and influenza, and more rarely pulmonary tumor and Hodgkin's disease, should be borne in mind.

51. Sero-diagnosis has afforded little help in diagnosis.

52. No modification of the tuberculin tests as yet devised differentiates clearly clinical tuberculosis that demands vigorous treatment from non-clinical tuberculosis that requires only a God-fearing life.

53. *Apart from tubercle bacilli,* two or more of the following five data are necessary for a positive diagnosis while the absence of all five is necessary for a negative diagnosis of pulmonary tuberculosis:

1. Tubercle baccilli in the sputum
2. Hemoptysis of a drachm or more due to no other cause
3. Pleurisy with effusion due to no other cause
4. Moderately coarse râles above the third rib and third vertebral spine, and
5. Mottling, irregularly distributed (a parenchymatous lesion) in the same area on a well-taken film.

53. It may be impossible to determine definitely the presence or absence of clinical tuberculosis, even after a study of two to three weeks.

II. Prognostic Theses

1. The uncertainties of prognosis decrease rapidly after the first year of disease but are ever present.

2. He who promises a patient what is unattainable injures himself more than the patient.

3. He is most dogmatic who verifies least often his prognosis. Dogmatism and brief observation are boon companions.

4. Recovery in pulmonary tuberculosis like recovery in carcinoma, can occur in the apparently hopeless, but does occur very rarely.

5. Whether physician or patient, he who is deceived by the "false convalescence" of Laennec, justifies the use of the term.

6. Whoever suffers relapse from unavoidable adverse conditions does better than he who relapses without discoverable cause.

7. The prognostic significance of race depends more upon the habits of

the individuals than upon other racial characteristics.

8. Resistance to clinical disease, largely lacking up to the fourth month of life, increases from the first year onward, and from about the sixth to the fourteenth year is stronger than in adult life. It may persist into old age, when, however, the recuperative powers are at a low ebb.

9. Lack of self-restraint often spells death.

10. Puberty and the menopause have less bearing upon the disease than pregnancy, especially repeated, frequent pregnancies, and hence marriage for women increases the uncertainties.

11. Tuberculous parents (when the child is under 3 or 4 years of age) increase incalculably the chance of infection. Hence the exposure to family infection has often been transferred to inheritance, which beyond this exerts no definitely proved influence.

12. The mentality and characteristics of the patient's family, their ability and willingness to help in his recovery by self-sacrifice over long periods of time, are most important. Therefore, recovery in the midst of the family is the most favorable recovery.

13. Poverty snatches recovery from the grasp of many a patient but money is only an adjuvant, not a means to cure.

14. He, who has worked indoors, does better under treatment, ceteris paribus, than he who has always seen the light of the sun in God's fresh air.

15. He works longest who works easiest, that is, he who returns to his former occupation when congenial and not complicated by sudden great effort and so makes his living with least exertion and worry, avoids relapse most often.

16. Recovery in a climate in which a patient is to live, especialy if accomplished at home, bespeaks greater longevity than immediate change of climate on arrest of disease. Climate may be only a minor factor in this effect.

17. He who is methodical and not lethargic, cheerful and not over sanguine, firm and not stubborn, educated about relapse and not ignorant of nor indifferent to the mistakes and failures of others, self-reliant and not selfish, possessed of imagination and of self-control in the worship of Bacchus, Venus and Mercury, grasps easily and surely his problem and solves it more successfully.

18. A sudden onset with acute symptoms bespeaks an earlier diagnosis than an insidious or catarrhal onset and hence treatment is begun earlier and life is more often prolonged.

19. An acute onset with extensive signs of disease or with severe and protracted symptoms points to a prolonged illness or to an early fatal termination.

20. The consumption of the body, with or without fever, indicates that assimilation is failing, and when steady and continuous is a priori evidence of poisoning of the body cells, betokening a serious outcome.

21. The continuous gain of weight on an ordinary diet is an indication of favorable progress but can occur with advancing disease.

22. Assimilation depends primarily upon ingestion, and "poor eaters" with

strong antipathies to milk, eggs, and meat, do badly.

23. Digestion is the keystone of the prognostic arch.

24. Fever is the most certain symptomatic sign of progressive disease and its chances of disappearance are inversely proportional to the length of time it has persisted.

25. Persistent high temperature under appropriate treatment is grave.

26. Frequently recurring febrile attacks, even of short duration, indicate advancing disease.

27. A subnormal temperature when other things are favorable is of little moment, especialy in cold climates.

28. The pulse rate, together with the temperature and weight, form the prognostic triad.

29. A pulse rate constantly over 100 when the patient is at rest in bed is of bad omen when not due to digestive disturbances.

30. Hemoptysis as an accident in the course of the disease is of little moment but when accompanied with fever, cyanosis, dyspnea, or tachycardia, is most grave. It is a favorable sign only when at the onset it fills the patient with the fear of God and a determination to obey orders.

31. The outcome depends as much upon what the patient has above his collar as upon what he has below it.

32. Nervousness that leads to marked dyspepsia or to excessive fear leads also toward the grave.

33. Dyspnea may be the only pronounced symptom of acute miliary tuberculosis of the lungs.

34. Uncontrollable excessive cough is the worst form of over exercise and favors a quick deterioration of the bodily resistance.

35. Cessation of menses indicates a weakening of the vital forces; a return of them an increase.

36. No urine or serum test is of prognostic value in early tuberculosis, but at times the urochromogen or diazo reaction may afford some aid in far advanced stages.

37. Arneth's polymorphonuclear picture, Medlar's leucocytic count, Westengren's sedimentation test have helped some workers.

38. A positive skin tuberculin test under the age of two indicates often an active tuberculosis. In youth, adult life and old age no tuberculin test differentiates clearly and surely active from arrested disease.

39. Physical signs tell by inference what has happened in the lungs, symptoms what is happening. The general condition is more important in prognosis than the physical signs or the history.

40. The most certain thing about the physical signs of "activity" or "softening" is their uncertainty.

41. Disease at an apex usually heals more readily than disease located elsewhere, but it must be in the real anatomical apex.

42. Extent of disease usually registers the time element; intensity the acuteness.

43. Extent of disease postpones arrest longer than localized intensity.

44. Extensive disease with short duration of symptoms suggests prolonged presence of the disease and possibly weakening of the resistance.

45. Scattered foci, discovered soon

after the onset of symptoms, betoken lack of resistance.

46. Granting the diagnosis, slight deviations in breathing or percussion are the most favorable physical signs.

47. The condition of the opposite side in advanced disease affects seriously the prognosis.

48. Increase of physical signs, with lessening of localizing and general symptoms and gain in weight, does not necessarily indicate an advance of disease.

49. Improvement and even arrest can occur without change in the physical signs.

50. Serial roentgenograms reveal best the progress of the disease.

51. He usually does best whose serial roentgenograms,—other things being equal,—show no further change.

52. Prognosis is more uncertain as long as the roentgenogram indicates change in the process for worse or even for better.

53. Mottling with soft cottony edges on a well-taken roentgenogram is very often associated with a recently active process and hence demands a more guarded prognosis.

54. As soon as the disease-process extends from the apex below the third rib, the seriousness of the case greatly increases.

55. A cavity detected only by roentgenologic study is less serious than one discovered by percussion and auscultation but both are serious.

56. The greater the quantity and possibly the greater the fluidity of the sputum, when persistent, the less favorable the prognosis.

57. Tubercle bacilli in the sputum indicate bronchial ulceration and the larger the number possibly the greater or more acute the ulceration, but enormous masses may occur in favorable cases.

58. The arrangement of the tubercle bacilli in clumps, chains, parallel pairs, or their occurrence in phagocytes is of uncertain prognostic moment.

59. Pneumothorax is always serious and often ushers in a fatal stage of the disease.

60. Secondary tuberculous enterocolitis, detected early, and treated appropriately, often retards but slightly the recovery.

61. Duration of treatment of less than three months is of little permanent help, while three or four years of treatment may assure an arrest.

III. Therapeutic Theses.

1. The tendency to recovery in some patients is so marked that it ensues in spite of the most injurious treatment.

2. That disease is rare for which the medical profession can do as little as for steadily advancing acute pulmonary tuberculosis.

3. The treatment of pulmonary tuberculosis demands little knowledge of drugs but much about the immediate and prolonged education of the patient.

4. Whatever advantages the sanatorium, and the class system and certain physicians possess, and they are many, lie in the fact that these institutions are really teaching institutions and the physicians are educators.

5. The marked tendency to temporary arrest or quiescence even in advanced stages rests upon the brow of

the tuberculous evil doer like the curse of Cain.

6. The danger time in tuberculosis, the perils of the "false convalescence" of Laennec, can not be over emphasized.

7. The idea that pulmonary tuberculosis, though often easily arrested, is a most curable disease, is a fallacy.

8. The time allotted to treatment is usually too short, for recovery is ever longer than onset. The value (possibly the results) of treatment increases as the square of the time, that is, two years are four times as valuable as one, but the struggle lasts often from diagnosis till death.

9. The physician must always bear in mind that he can influence the lungs only through the intermediary of the body. Hence besides being an educator he must become an expert in physical training.

10. The physician must have imagination, sympathy, firmness, approachableness, as well as knowledge of the disease of the individual patient, his psychological and his sociological condition, and last but not least, of the limitations of his own knowledge.

11. Few physicians are temperamentally suited to successfully care for chronic disease, while many can treat successfully acute disease. Pulmonary tuberculosis is a chronic disease.

12. The patient is worried, confused, twists what is told him and can master the thousand and one details only by repeated perusals of directions carefully written down. He should not be blamed for the physician's mistakes of omission. Word of mouth, however, conveys to the patient emphasis and force and directness that tons of tomes cannot.

13. At home and abroad, in the desert or on the ocean, in the lowlands or upon the mountains, patients may do well, as they recover anywhere and everywhere, for it matters less where than how they live.

14. Fresh air, one hundred times more frequent outside than in the house, depends for its value far more upon the temperature, moisture and movement of the air than upon the presence of any organic or inorganic constituents.

15. The skin demands better air than the lungs, for we can breathe with impunity far worse air than we can live in. Hence the lungs are benefited by fresh air no more, no less, than any other organ.

16. The dose of fresh air, an important component of the vis medicatrix naturae, must be carefully regulated for the weak and aged, as stimulation, not fatigue, is the goal.

17. The development of a fresh air conscience which suffers, when its owner crosses too soon the threshold into the house, aids greatly in recovery.

18. For those who spend eight hours out of doors, sleeping out does not hasten recovery, providing they sleep in well ventilated rooms, but for those forced to be indoors during the day it may be a sine qua non of continued arrest.

19. The sanatorium, the best place in which to treat patients in large numbers, has shown that permanent arrest may follow effectual treatment; the hospital has afforded evidence that direct contagion may in part be con-

trolled, while the dispensary has become the advanced attacking line, so to speak, that carries the warfare into the enemies' camp, that is, into the homes of the tuberculous, and disposes of the wounded in a proper manner.

20. The length of stay in these institutions depends upon the object to be attained; for permanent recovery two or three years; for quiescence at least three months; for prevention of infection by far advanced cases, as much as possible of the time between admission and death.

21. Give your patient as little food as will serve his purpose and have clearly in mind what this purpose should be—to gain up to, and ten to twenty pounds beyond his usual weight, which is generally ten pounds under what he should weigh for his height and age.

22. Remember that too much food may in the end prove as disastrous as too little food, and furthermore that it is a great pity to waste good food.

23. See that your patient has a well balanced ration and if you wish him to gain weight, increase his carbohydrates.

24. When anorexia appears upon the horizon, and simple tonics cannot dispell the bugaboo, do not fail to resort to fluids and fluids only without a bite to chew.

25. Injury demands rest for repair. Scar tissue forms but slowly.

26. Insistance upon absolute quiet and its observance for six weeks affords rest for repair, time for growth of scar tissue and opportunity for the walling off of areas of disease in the early afebrile stages. Such short periods of rest in later stages accomplish no comparable results.

27. When such a period of rest has been enforced, exercise can be more quickly increased with less danger of relapse.

28. While differences of opinion may exist in regard to the explanation of how rest brings about recovery, none questions its efficacy.

29. The period of preliminary rest affords the physician opportunity to assist the patient to think out his problem, which means, when it has been successfully done, that half the battle has been won.

30. When general bodily rest fails to aid in arresting the disease, many methods to bring about increased local pulmonary rest have been devised and in many instances have accomplished an arrest of the disease (e.g., posture, weights on the chest, various harnesses, phrenicotomy, artificial pneumothrorax (including pneumolysis) and thoracoplasty).

31. Exercise should be regarded as a powerful and a dangerous medicine, to be used carelessly never, with impunity by none, and as a deadly drug by all.

32. Work for therapeutic purposes is fraught with much danger and is more safely replaced by work which fits the patient for his future (often his former) occupation.

33. Since the vast majority of patients must or do seek treatment only in the climate in which they contract the disease, the so-called climatic treatment is of importance to hardly more than five per cent of all patients.

34. Change, change of food, change of work, change from work to rest,

change of environment, change of climate, in fact any change that stimulates nutrition sufficiently, helps toward recovery.

35. Those with acute tuberculosis, cachexia, marked dyspnea with cyanosis, advanced nephritis, diabetes with carbohydrate intolerance, intractable diarrhea, extensive laryngeal tuberculosis with dysphagia, or tuberculous pneumothorax are best treated for a time at least in a hospital near their homes.

36. It is criminal to advise an untrained patient to seek benefit from climatic change without constant medical supervision.

37. Resilient youth responds to strong stimulation while more rigid age requires protection.

38. As a rule a patient should be sent to as cold a climate as he can react to and enjoy.

39. Beyond the empirical fact that many patients do better for some change, much has been written but little proved about climatic treatment.

40. Climates of high altitudes unquestionably exert the greatest physiologic effect upon the human economy.

41. There is as yet no accredited specific (like arsphenamine in syphilis) for tuberculosis.

42. Drugs may alleviate or even remove for the time being certain localizing and constitutional symptoms but affect in no direct way the disease that produces them.

43. Hemotherapy and organotherapy have only historic interest, while serotherapy has greatly disappointed many of its most ardent followers. Zomotherapy may be an exception but it is to be used rather as a food.

44. Bacteriotherapy, that is, the injection of attenuated (for the species), living tubercle bacilli has given the most promising results so far but immunity so produced is not lasting and not yet safely applicable to man. The use of antagonistic bacteria (like the seton of old) is chiefly of historic moment though the activation of one tuberculous focus may bring about quiescence in another.

45. The tubercle bacilli or their products, otherwise known as tuberculin, the most widely used of all so-called specific agents, have not given, when subjected to cold impartial statistical study, the results claimed by the enthusiasts.

46. In a few cases remarkable recoveries occur in patients taking tuberculin, which are apparently more than coincidences and tend to keep alive the treatment.

47. The time may yet come when by the study of the sera or other means we may be able to select the proper antigen and so to space and to grade the dose, that, having removed tuberculin from the field of empiricism, we can use it more successfuly in the treatment of certain cases of tuberculosis.

48. The use of the heavy metals and rare earths in treatment is associated with risk and the results, while striking at times, are uncertain.

49. He who deals with statistics upon which the lives of others may depend should have more knowledge of statistical work than will suffice only to compute averages and often erroneously to compare them.

Some Fundamental Clinical Aspects of Deficiencies*

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Introduction

Toward the close of the nineteenth century, as the sciences of bacteriology and immunology were becoming well established the dawn of knowledge arose concerning the enormous importance of small amounts of chemical substances for the maintenance of health. It is known today that abnormal amounts, or an improper balance, of highly potent active principles derived from glands of internal secretion, and of vitamins, of inorganic and other substances contained in food, can lead to many sorts of disorders. The secretions of the ductless glands together with materials derived from food must form with blood a suitable environment to bathe the cells of the tissues. This nicely balanced mixture may be altered in myriad ways and if too unsuitable the cells suffer and disease ensues.

Ill health or disease arises either because the organism is affected by the presence of something harmful or lacks something beneficial. Infections, intoxications and excess of substances are examples of the reasons for the former sort of condition. The term "deficiency disease" has been applied by custom to conditions where the essential cause is an inadequate supply of accessory food factors known as vitamins. Deficiencies, however, may be due to a variety of causes acting individually or combined. They may develop among other ways from the lack of an ingredient necessary for the manufacture of a specific molecule (hormones), from disease of organs leading for example to anoxemia and to failure of supply or manufacture of such substances as enzymes or bile. The lack of an element as iron, calcium and iodine, insufficient food or water, or the inadequate supply of protein, certain amino acids and other food components also can lead to a deficiency disease just as much as the lack of vitamins.

Injurious effects also can be dependent upon excesses of some factors that in sparse amounts lead to a deficiency disorder, for example excess of protein, hormone secretions and the ingestion of too much irradiated ergosterol (vitamin D?). Thus, for health, the body always requires *optimal amounts* of materials and the absence of harmful factors.

Disorders due to excesses of food, to intoxications and infections, have

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received more attention and are better recognized than many deficiencies. States of deficiency however, are very frequent and those wholly or partially due to deficiency, or mal-adjustment of quality or quantity of one or more factors obtained from food, are much more common than usually is appreciated. Ill health may be produced by deficiency of a food factor in much smaller amounts than necessary to create the typical syndrome associated with its lack. The effects of a persistent slightly faulty diet may become detectable only after many years and perhaps not for generations. The earlier evidences of disease from unsuitable food have been studied but little and demand the attention of clinicians.

All aspects of deficiencies cannot be discussed here. My remarks will be confined to a few concerning particularly nutritional deficiencies.

Some Historical, Philosophical and Generalized Aspects

Descriptions were given of disorders due to excess and deficiency of internal secretions and to lack of vitamins long before there was recognition of these products from little chemical factories of marvelous ingenuity, and products capable of miraculous effects. Murray's discovery in 1891 that an extract of sheep's thyroid gland benefited patients with thyroid deficiency was one of the first to open up the field of endocrine therapy. The activities of John Huxham, of James Lind and Captain Cook in the eighteenth century in preventing scurvy pointed the way to the knowledge of today concerning the lack of vitamin C. In referring to the influence of food for scurvy patients "to supply the elements wanting in their spongy tissues" Oliver Wendell Holmes[18] in a lecture given in 1861 made the following prophetic statements: "I have recognized that the perfection of art is often a return to nature and seen in this single instance the germ of innumerable beneficent future medical reforms." He continued: "I cannot help believing that medical curative treatment will by and by resolve itself in a great measure into modifications of food swallowed. . . . The effects of milk and vegetable diet, of cod liver oil . . . are only hints of what will be accomplished when we have learned to discover what organic elements are deficient or in excess in a case of chronic disease and the best way of correcting the abnormal condition." Cod liver oil was used for invalids in the eighteenth century. It was recorded in 1807 as of value in osteomalacia (Bardsley)[14] and in 1822 as a cure for rickets (Shutte), and yet it was about a century later before its therapeutic properties were truly comprehended. The importance of iodine and its therapeutic value in "goitre" was demonstrated in 1821 by Coindet and here again about one hundred years elapsed before the significance of iodine was appreciated. These remarks indicate how long it may take man to grasp the significance of observations. One must always be prepared to recognize that but a hair above the underbrush may mean that a large mammal is at hand.

Since the pioneer work of Eijkman (1897), Grijns (1901), Hopkins (1906) and Funk (1911) on vita-

mins, of Schiff (1859) and many others on internal secretions and of various investigators on the importance of inorganic elements, complete proteins and other substances in the diet, knowledge concerning these matters has progressed with startling rapidity. Even so, today's comprehension of a deficiency of many such substances, like the title of Holmes' lecture is but "Border Lines of Knowledge in Some Provinces of Medical Science" and is for revision tomorrow as progress will occur to upset today's erudition.

With the advent of new knowledge there is a tendency for the physician to attempt to apply it to a host of disorders. Undoubtedly many patients have received all sorts of glandular, vitamin, tissue extract and inorganic products which could not benefit them. Others that could be benefited by such products have had them prescribed in too small or too great amounts. This is partly because with the haste of modern life there is a tendency to avoid studying patients in a scholarly way, and to neglect the precise advice of qualified students. Furthermore the physician often does not have knowledge whether a given preparation has been proved to have potency. He is apt to be induced by the laity to try new therapy, since the public has appropriated knowledge of vitamins, of other food elements and of glands of internal secretions, before investigation has been concluded. Often these factors are considered the cause of all evils and there have arisen more or less fanatical ideas about them.

There is a growing danger in the tendency to attribute every nutritional disorder to vitamins. One must remember that a well balanced adequate varied diet is of prime importance for health; a matter appreciated by the ancients and alluded to by such a pioneer as Lewis Cornaro, the Venetian who died in 1566, and whose book reached the fortieth English edition in 1821. Even if a patient's disease calls for a reduction of some type of food, the diet must contain at least a minimal requirement of all necessary elements. I have seen, as have others, improper dietary treatment lead to deficiency disorders; for example make patients with nephritis suffer from protein deficiency, those with duodenal ulcer develop scurvy, women with digestive symptoms become anemic from lack of iron in their food, and even beri-beri arise in a child fed by a physician's advice on three types of canned food.

Much of our knowledge concerning deficiencies, especially of vitamins, has been derived from experimental animals where one factor at a time can be varied. Although one often may interpret results obtained with animals as comparable to what may take place in man, the clinic must be the place where final knowledge concerning human beings is to be obtained. Deficiency diseases in man may have a complex etiology and dietary defects are often not alone the lack of vitamins, but complicated for example by incomplete or low protein intake, excess of carbohydrate, infection or by altered physiological mechanisms. Some of the outstanding disorders due to vitamin deficiencies in man are well recognized and have been studied critically. Clinical studies concerning nu-

trition comparable to those on animals are few and progress may be expected by the study of patients and the isolation by chemists of factors that in small amounts are so important for health. By carefully controlled and prolonged observations on patients one may expect to learn not only more about the clear cut deficiency diseases, but also much about conditions that represent abortive, incomplete or border line states of deficiencies. Probably many such conditions are not recognized but gradually will become so. Investigation will add knowledge about certain diseased states not due primarily to deficiencies, but which can be in a measure prevented or alleviated by supplying the proper amount or balance of factors, which if incorrect can cause a nutritional deficiency disease.

Trained clinical investigators may help to unravel such problems as the influence of factors on the absorption or utilization of vitamins and the quantity of vitamins desirable to have stored in the body, but these matters among many others deserve scrutiny by every practitioner of medicine. A great deal may be learned from skillfully taken dietary histories, observations on habits and the influence of feeding given substances in large amounts for sufficient time.

Partial Deficiency

Diets are rarely selected by man so as to present the possibilities of clear cut dietary deficiency disorders as are encountered in experimental animals, but man undoubtedly often selects his food unwisely and obtains an undesirable diet that may lead to defects from a prolonged consumption of a suboptimal amount, or an improper balance of factors essential for health. It is disorders from long continued undesirable diets causing effects slowly over years or in a second generation that the clinician must watch for, rather than readily recognized defects from grossly abnormal diets taken over longer or shorter periods of time.

Confusion must not arise because deficiencies of two sorts occur in the same patient. We have observed the association of scurvy and true pernicious anemia, also of pellagra and pernicious anemia, the former being alleviated by a yeast concentrate and the latter some weeks later by potent liver extract. Furthermore a deficiency disorder due to food defects may occur in patients with a deficiency of an internal secretion and such cases offer matters for interesting speculation.

McCollum,[30] McCarrison[27] and others have pointed out how with the advance of civilization it is common to find people choosing diets composed of "ready to serve" or "grocery store" foods as those prepared by high heat, milling, canning, salting and the like, together with excesses of concentrated carbohydrate foods and sugar, with the omission of the so-called protective foods: fruits, vegetables, milk, and the organs of animals. Such diets obviously are undesirable and often do not contain optimal amounts of vitamins, and as McCarrison[25, 26] has suggested may be one reason why gastrointestinal disorders among highly civilized people are more frequent than among those living an aboriginal life. The rôle played by such diets in producing dental defects, decreasing re-

sistance to infection and inhibiting physical fitness and growth are recognized. Although disorders resulting from improper food may appear to be slight, under such circumstances they may slowly lead to altered functions or anatomical changes which permit organisms or other factors to be the more immediate cause of disease.

Deficiencies are more readily produced during growth, so one would expect to observe the effect of partial deficiencies more often in children than adults. Apparently in Europe and North America there is an increase of defective nutrition among children which can be attributed sometimes to the mother's diet and in other instances to the child's. McCollum[30] and Mellanby[31] have emphasized this and suggested that many border line cases of malnutrition are due to suboptimal amounts of particular substances. Hoobler[19] has given evidence that it is not uncommon for pale and undeveloped, fretful infants with anorexia and spastic muscles to suffer from partial vitamin B deficiency, a condition readily alleviated by the ingestion of "yeast vitamin B concentrate." The role that vitamin B plays in stimulating the appetite sense, as first shown in dogs by Karr[20] and later Cowgill[7, 8] is for clinical consideration and many observations should be made concerning the part played by this factor, or some part of it, in the nutrition of the nervous system. It is to be recalled that every sort of nervous disorder is more common among civilized than non-civilized people, and although there are many reasons for this one may wonder what rôle, if any, is played by inadequate diet and lack of specific dietary factors.

Oftentimes it is not simple to elicit from the patient that his diet has been a defective one—a matter emphasized by that illustrious student of pellagra, the late Dr. Joseph Goldberger, who did much to aid mankind and whose studies demonstrated that lack of the —P.P.— factor of vitamin B causes pellagra. In response to casual questions the patient is apt to reply, for example, "Yes, I eat meat and green vegetables," but upon careful questioning the amount will be found to be trivial or the form peculiar. Furthermore one must recognize that individual constitutions, with known or unknown defects, may explain why one person readily develops a deficiency disorder on a given diet and another does not. A condition favoring the development of a deficiency disorder may be obvious; for example partial intestinal obstruction may permit pellagra to develop easily and pernicious anemia has been associated with the same cause. Likewise chronic alcoholism favors the development of pellagra and some other deficiencies. The rôle that the gastric achlorhydria induced by alcohol may play in the development of such conditions is referred to further on.

Illustrative Cases of Partial Deficiency

Two examples are cited below to illustrate further the nature of border line cases of deficiency disease or partial deficiencies arising in adults.

A woman, 45 years old, who has always lived in Massachusetts had experienced for 15 years symptoms of

colonic indigestion. On reflection the case may appear simple to diagnose, but as she had consulted a large number of physicians without obtaining the diagnosis I offer or without relief it is evident that the condition is not well understood. In spite of trying "all sorts of diets" her gastro-intestinal symptoms continued and increased, though they were less when she was forced to take a little steak. Gradually she lost weight and muscular weakness became prominent. A *secondary* anemia with hemoglobin 60 per cent developed. Leading questions brought forth the fact that in May, two years before she was seen, she had "an insignificant generalized eruption on the back of her hands from her wrists to her knuckles, that later peeled" and that this recurred to a trivial degree a year later. This area of her skin appeared slightly more pigmented than her finger tips or arms. All sorts of tests yielded no further significant information except that she had achlorhydria. At first she described her diet in such a way as to suggest that it was satisfactory, but it was soon learned that although there was set before her a nutritious diet she had always been fussy and particular about her food. In spite of special diets and having eaten a little of many sorts of food, for years she had eaten much dextrinated food, many French and English biscuits prepared for invalids. For years meat had been eaten scantily and only when cooked for an unduly long time, while fruits and green vegetables had been taken in never more than minimal amounts particularly in pureed form without cream. The patient was fed daily for two weeks no other food than 225 grams of calves' liver—a food rich in many elements including the P.P. factor, a component of vitamin B—; one orange and 70 grams of bread. With startling rapidity all her symptoms of many years duration vanished, and now for two years she has been on an ordinary well balanced diet and remained in complete health. This case illustrates a form of pellagra where the defective diet led particularly to gastro-intestinal symptoms and only after years permitted the appearance of the mild skin lesions.

Patients with pernicious anemia often have gastro-intestinal, as well as at times central nervous system symptoms, long before there is evidence of anemia, and it is then that they should receive liver treatment rather than when anemia becomes pronounced. Cases of this sort may be considered border line ones of a deficiency disorder. A clear cut example is the case of a man whose two older brothers have pernicious anemia. His blood repeatedly showed no signs of anemia, but achylia gastrica was present. For years he suffered from intestinal symptoms and often for weeks at a time would have from one to three stools a day. Muscular weakness and vascular hypotension were features as were ill defined "neuritic" pains in different parts of his body. There were however no symptoms confined to the hands or feet or referable to disease of the central nervous system. For a month he was fed a diet rich in muscle meat without improvement. Then for a month he took a normal diet with large amounts of both wheat germ oil and a yeast con-

centrate, thus supplying him with large amounts of both parts of vitamin B (vitamin F and G). On this regime he became perhaps slightly better. In the third month he continued with the same diet and took large amounts of a liver extract rich in the substance effective for pernicious anemia. Within the month his whole sense of well being improved extraordinary and his gastro-intestinal symptoms vanished. He has continued for 18 months to take liver extract and a normal diet and his symptoms have not returned. Not only are there probably comparable cases to be alleviated, but many individuals with similar symptoms, who can be benefited by following out the prescription of an adequate well balanced diet:—for example many young women eating "soda fountain counter lunches" and obtaining a hastily swallowed scant breakfast, who suffer from slight simple anemia and gastro-intestinal symptoms.

Deficiency From Inadequate Utilization of Substances After Their Ingestion

An individual may ingest a sufficient amount of material to prevent a dietary deficiency disorder, but in spite of this the disorder may develop if his organs are unable to utilize or prepare the necessary substance. That adequate amounts of absorbed vitamin may not be utilized by the body is suggested by Kunde and Williams'[22] animal experiments. Their studies suggest that vitamin D, even in large amounts, can not prevent the development of rickets in cretin rats. Perhaps such a condition as severe arteriosclerosis may act to precipitate symptoms of deficiency in the presence of an amount of active principle sufficient in health for the avoidance of symptoms. Damage to the blood vessels could prevent cells from obtaining readily a suitable supply of an active principle. Observations by Dr. Weiss and myself suggest that an abnormal condition of the vascular system may be one that favors the development of scurvy in adults and hinders the effect of the substance effective in pernicious anemia.

Impaired digestion may prevent the proper absorption or assimilation of vitamins. Probably deleterious effects from taking below optimal amounts of vitamin B and C are enhanced by lack of absorption or the influence of intestinal bacteria, when the food is improperly balanced, especially when associated with an excess of carbohydrate. The antagonistic action of something in certain fats and oils which counteracts the curative effect in animals of vitamin E is noted by Evans and Burr;[10] and Mattill[24] has observed that oxidative changes within the intestine can decrease the potency of given amounts of vitamin A. Ferrous sulphate[9] also can act to destroy vitamin A. On the other hand there are factors that can favor the action of a vitamin. Sunlight can do this. Evans and Lepkovsky[11] have noted that it takes less vitamin B to protect animals when fat is present in the diet than when it is not; and there are other observations to suggest that certain combinations of substances enhance vitamin activity. Other facts are available to indicate the importance of supplying a lacking substance with a

well balanced diet containing nothing to hinder and perhaps something to favor its action.

The Role of Achylia Gastrica

Inability actually to obtain or digest from food a substance necessary in small amounts for the maintenance of health has been demonstrated by Castle.[5] His work in an epoch making contribution to human gastric physiology and towards the understanding of the disease pernicious anemia, in which gastric achlorhydria even following the injection of histamine practically always occurs long before and after treatment. Castle has shown conclusively that whereas the daily feeding of 200 grams of beef steak produces no effect on the pernicious anemia patient, this amount of beef steak when digested for about an hour in either a normal stomach or in vitro with normal gastric juice and then fed daily to the patient produces effects entirely like those seen with liver therapy. On the contrary no benefit occurs from the feeding of beef steak digested with only commercial pepsin and hydrochloric acid. This work clearly indicates why achylia gastrica can play an important rôle in the development of pernicious anemia.

The frequent occurrence of gastric achlorhydria in various deficiencies tempts speculation concerning its influence. There are few observations as to whether or not achlorhydria, if present, persists after histamine injection in other deficiencies than pernicious anemia and this matter is worthy of study. Undoubtedly in many cases achlorhydria develops as the result of a deficiency, but in pernicious anemia it occurs before obvious signs of the disease appear and it may in other sorts of deficiencies play an etiological role. Achlorhydria in scurvy of adults is common, but free acid often returns as the patient gets well. In myxedema, hypopituitarism, diabetes mellitus and Addison's disease achlorhydria is not uncommon. It is found with great frequency in pellagra and often persists after the patient's symptoms are alleviated. The condition occurs in beri-beri and has been reported to develop sometimes in animals fed diets deficient in vitamin B.

It is recognized that chronic alcoholic patients develop gastric achlorhydria and are potential pellagrins, as they appear more susceptible to pellagra following an insufficient diet than those who are not addicted to alcohol. It seems that pernicious anemia also may be aided to develop by chronic alcoholism. Cases of peripheral neuritis, yet not considered beri-beri, associated with vitamin B deficiency have been reported[13] and gastric achlorhydria may accompany multiple neuritis. Dr. Castle and I have noted that the two diabetics we have observed recently with peripheral neuritis had achylia gastrica and their symptoms slowly improved upon taking large amounts of a concentrate of yeast. With these facts in mind and the recognition that vitamin B deficiency leads to disorders of the nervous system one must wonder if achylia gastrica is not a factor that can inhibit the utilization of both the P.P and anti-neuritic factor of vitamin B. It may be recalled for data upon which to build hypotheses that the pathologi-

cal changes in the spinal cord in pellagra may simulate entirely those found in pernicious anemia. The work of Boyenval[3] and Koskowski[21] on animals is also of interest in this connection. They have shown that if rats are fed vitamin B deficient diets and given injections of histamine that they do not develop the premortal nervous disturbances observed in control animals. These thoughts and facts suggest that an elucidation may be arrived at from carefully made and controlled clinical observations upon patients with gastric achlorhydria and symptoms even of a trivial sort referable to the nervous system.

The Rôle of Balances Between Vitamins and Other Substances.

The balance of factors or the relative proportion of each is often a more important aspect of biological mechanisms than the presence of an absolute amount of a given substance. The interrelationship of the glands of internal secretion and the influence of some of their secretions upon metabolities is recognized. There is little knowledge concerning the importance of vitamin balance and the effect vitamins have on inorganic metabolites or vice versa, upon hormones and so forth. Such matters can be studied in the clinic while progress is made in the laboratory. Burrows[4] has suggested that when vitamin A predominates greatly over vitamin B the growth of cancer is delayed and hastened under opposite circumstances. The effects of well-balanced diets rich in vitamin A and sparing in vitamin B are difficult to evaluate in man, but are worthy of study. Perhaps the recognized influence of vitamin A to increase resistance to infection is enhanced when its balance with vitamin B is of a given sort. In such a condition as chronic hypertrophic (osteo) arthritis one may wonder what rôle, if any, is played by vitamin balance within the body. In such a consideration one should recollect that metabolic changes, or those due to infection or altered digestion, could be in themselves but the expression of a disorder favored by an unsuitable soil existing for years dependent upon the consumption of food factors in non-optimal quantities. One may ask is it possible that in man the genesis of certain urinary calculi can be attributed to an imbalance between vitamins and organic metalbolites, which is suggested because vitamin A deficiency in rats, as Osborne and Mendel[24] first noted in 1917, induces the development of calculi, but marked vitamin A deficiency is rare in man.

The effect of vitamin D upon the metabolism of calcium is classic and it is probable there are various other comparable mechanisms in the body. In fact, McCarrison[28] has hinted at a relationship between manganese metabolism and the vitamins. Under certain circumstances the feeding of liver and iron can produce a greater effect on blood formation than either alone. Hart and his associates[16] have shown that copper enhances the action of iron in the formation of hemoglobin in rats rendered anemic by a milk diet and copper can be a catalyzer of value in avitaminosis[6]. The supplementary effect of one substance upon another is undoubtedly an important one to not lose sight of. There is

probably, at least under certain circumstances, an important quantitative relation of vitamin B to protein intake as shown by Hartwell's[17] studies on the mammary secretion of rats.

It is possible that there is some optimal balance between some vitamins and some hormones. However, it is known that vitamin deficiency can affect glands of internal secretion, for example, it is recorded that lack of vitamin B increases the size of the islands of Langerhans[1] and hypertrophy of the suprarenals[12]. It is also stated [32] that vitamin B may decrease the blood sugar in diabetes mellitus. Changes in the thyroid gland can result from vitamin deficient diets in the presence of sufficient iodine [29 15]. The complexity of the many possible interrelations of substances, the lack of which lead to a deficiency disorder, has been alluded to, simply to indicate the desirability of thinking broadly, and to recognize there are many reasons for therapeutic results and many ways they may be brought about.

Infection in Deficiency Disorders.

Infections can intensify and precipitate the symptoms of a deficiency disorder which is important for the clinician to appreciate. Their effect is one of other illustrations concerning the similarity of behavior between vitamins and hormones. Mild, often temporary, states of hypothyroidism and decreased function of other glands of internal secretion occur following infectious disease, such as influenza, pneumonia and typhoid fever. Infections may be responsible for pronounced dysfunction of the glands of internal secretion. Vitamin deficiency disorders too, may be precipitated in the wake of an infection. This serves to stress the importance for individuals to maintain in their body optimal amounts of the necessary accessory food factors.

Infections arising in the diabetic are well known to lower his sugar tolerance. In myxedema patients, also, infections apparently intensify their deficiency. It is a striking fact that infections in untreated cases of pernicious anemia hinder the beneficial influence of liver. They are the chief cause of significant decreases of the red blood cells in such patients with normal red blood cell counts taking with regularity reasonable amounts of liver. Thus, in the presence of infection in these three conditions when the patients have been maintained in satisfactory health, it is often necessary in order to prevent progressive signs of deficiency to prescribe an increased amount of active principle. Likewise, when treatment is begun it will require the administration of larger amounts of active principle to obtain the best possible results than are necessary when infection is absent. A similar state of affairs apparently holds true for pellagra and probably for at least some other deficiency disorders. The exact mechanism of the effect of infection upon patients with deficiencies, but maintained in health by the daily administration of specific substances is yet to be explained. In seeking an explanation it is worth noting that there is some similarity in the chemical nature of the specific substances involved. The products are nitrogenous. The part of vitamin B that has been isolated, and, in all prob-

ability, the part that has not been isolated and the substance effective in pernicious anemia, which has basic properties, are small in size, as are thyroxin and adrenalin. The two latter are known to be relatively simple compounds related to the amino acids of food protein and probably derived from them. Insulin, like secretin is larger in size and a polypeptid.

Treatment With Optimal Doses.

It is a first principle of therapeutics to administer enough of a substance to obtain an optimal effect and to not be satisfied with improvement unless it is as great as possible. Untoward symptoms from excessive dosage are to be avoided. There is little knowledge about the effects of large doses or a long continued excessive intake of vitamins. It is known that too much irradiated ergosterol (vitamin D?), can soon lead to deleterious results and excess of anti-pernicious anemia substance in patients with this disease cause undesirably high levels of the red blood corpuscles. The dosage of some substances, the lack of which leads to a deficiency disorder is well understood, but little is known about others. Remarkably small amounts of products from nature's little chemical factories can do much good. It is evident, however, that the minimal daily quantity required by a normal person to protect him from deficiency is often much less than the optimal quantity for health or the amount required to alleviate satisfactorily a patient with a deficency disorder. In trying out new therapeutic procedures this should be borne in mind and also the principle of giving enough for a long time, even if in the form prescribed it seems excessive. Such treatment may lead to important results where failure appears from too small amounts. Our results with the liver treatment of pernicious anemia illustrate this [33]. The daily ingestion of 75 grams of liver will accomplish little and in some cases produce no effect, whereas 225 or more grams will cause rapid improvement. Blumgart[2] has studied in detail a woman with severe osteomalacia who showed no improvement at all after taking daily for 18 months about 20 grams of cod liver oil of high vitamin D potency. Her diet apparently contained at least an amount of calcium suitable for a normal woman. When she was given daily five times this amount of vitamin D and 2.0 grams of calcium, rapid progressive improvement took place which was hastened by the application of ultraviolet light. The clinical and roentgen-ray observations demonstrated that ossification of the bones had occurred. The patient is now well. The case points out again, as does the following example, the importance of adequate treatment. There is literature to the effect that large doses of iron can be effective where commonly prescribed doses are inert. Some recent observations made with several of my asociates indicate that although the normal body requires but about 15 milligrams of iron a day, distinct rapid effects are produced in certain cases of chronic secondary anemia, particularly those of obscure or dietary origin, when 350 milligrams of iron are fed yet insignificant or negative results may be obtained when 50 milligrams are ingested.

The degree of deficiency in different patients with the same disorder will vary so that each one must be treated individually. Although one may formulate general rules, as for example in pernicious anemia, that a certain amount of liver extract (the amount of liver extract No. 343, N. N. R. derived from 400 grams of liver) will produce good results in essentially all cases there are cases for which this amount is not, and others for which it is, optimal. Recently we have noted that rarely a much larger dose is required to obtain satisfactory improvement in the patient's health. The amount of a deficiency may depend in part upon the reserve supply of a substance in the body and it is important to carry out therapy so that if possible the individual has stored in his body an optimal amount of the material that he has lacked. The quantity of vitamin A in the liver of patients without symptoms associated with its deficiency has been shown to vary widely[23]. The relation of the amount of vitamins and other substances stored in the body to therapy and to disease is a problem for future study. The effect of factors favoring or inhibiting the action of a particular active principle is also not to be forgotten in prescribing for the patient.

It is important to appreciate that in deficiences of many types there exists a quantitative relationship, up to a maximum, between the amount of substance the patient receives and the degree of benefit that is derived from supplying the deficient material. A patient's health may be so greatly improved that the physician may forget to consider whether it is as good as possible. Citing again pernicious anemia as an example, I emphasize the importance of not being satisfied with red blood cell counts of 4 million per cubic millimeter, but to attempt to make the count normal. In a given patient without complications a certain sub-optimal amount of the active principle given daily will increase the red blood cells from a very low level to 3.5 million per cubic millimeter and maintain the count at about that number, but optimal daily amounts will permit the corpuscles to reach normal numbers and remain there. Furthermore the amount of liver prescribed should not be based on the red blood cell count alone, but upon this and all symptoms and signs exhibited by the patient, such as those referable to the digestive and nervous system and the character and size of the erythrocytes.

In treatment, thus, as for the maintenance of the best health, the physician must not be satisfied with an individual receiving enough material to prevent distinct symptoms, but must see to it that his patient secures suitable amounts and balances of all factors contained in food and those necessary for the maintenance of the best health that the individual can obtain. The physician should never forget to treat the individual himself and in prescribing particular substances never neglect to recommend other procedures for the patient's comfort and improvement.

Concluding Remarks.

In conclusion emphasis is placed on the following topics:

The importance of an adequate varied diet for man with optimal amounts of all necessary factors.

Many types of deficiencies may occur in man and dietary deficiencies are of numerous kinds.

The probability that sub-optimal amounts and balances of vitamins, minerals, amino acids and so forth taken over long periods of time favor ill health and incomplete growth and decrease physical fitness and the chances for longevity.

Lesser grades of deficiency disorders exist that are often unrecognized and may appear only after years of an undesirable diet.

Many factors, as infection, may operate to produce or intensify symptoms from a deficiency.

Improper diet may not be the cause of a deficiency arising from lack of material contained in food, because the individual may be unable to prepare or assimilate a required factor.

One should not think of vitamins, or substances the lack of which produce symptoms of deficiency, as causing only a particular disease or a special symptom but consider what tissues or functions they affect. Each plays its own rôle in the body's economies and tends to affect definitely certain types of cells or functions as is well illustrated by Wolbach's studies.

The proper treatment of deficiencies necessitates recognition that there is a quantitative relationship, up to a maximum, between the amount of substance the patient receives and the degree of benefit that he will obtain.

Vitamins and hormones and the lack or excess of other chemical substances are not the cause, nor will they cure, all evils. In time one will reflect that today's erudition concerning these substances was but "border lines of knowledge."

The laboratory does not supply something absolute, it increases the necessity for careful clinical study. In doing so, treatment with a sufficient amount of material is important for success. Final knowledge regarding deficiencies in man will be obtained by studying with adequate controls *homo sapiens*.

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Some Physiological and Biochemical Aspects of Deficiencies with Special Reference to Vitamin B*

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MUCH of the support for the vitamin hypothesis has come from the experimental laboratory of students of nutrition. The pioneer work in this field, however, had a clinical origin centering around the disease beri-beri. In his monographic study of this disorder Vedder (1913) championed the idea that the primary etiologic factor is lack of a vitamin substance. Many clinicians, however, especially among the Japanese (Ogato et al, 1923) hesitate to concur in this opinion, because experimental beri-beri in animals differs in certain respects from human beri-beri as seen in the clinic. Whereas the experimentally produced condition may be due to lack of one dietary essential, the case observed by the clinician is more likely to be the result of a multiple rather than a single deficiency. Consider "wet" and "dry" beri-beri (figure 1).

Each is characterized by the same neuromuscular symptoms. How may one explain the presence or absence of edema? Studies of edema indicate that this condition is associated with a low concentration of blood plasma proteins. By feeding diets low in protein for extended periods, edema has been produced experimentally (Harden and Zilva, 1918; Kohman, 1920). It is conceivable that cases of "wet" beri-beri are suffering not only from a deficiency of a particular vitamin but from a shortage of protein as well. The syndrome illustrated in figure 2 (Cowgill, 1921) is readily produced in dogs by feeding the animals with an artificial food mixture rich in protein and other dietary essentials but deficient in the antineuritic vitamin.

The condition of this dog is quite similar to that of "dry" beri-beri shown in figure 1. In this experimentally produced condition edema has never been observed; so far as known these animals lack only one dietary essential, namely the antineuritic vitamin.

The ideas advanced concerning the rôle of the individual vitamins reveal a variety of viewpoints, some attributing a general type of function involving every cell, others suggesting a more specific part in relation to certain organs or systems of organs. Vitamins have been conceived as indis-

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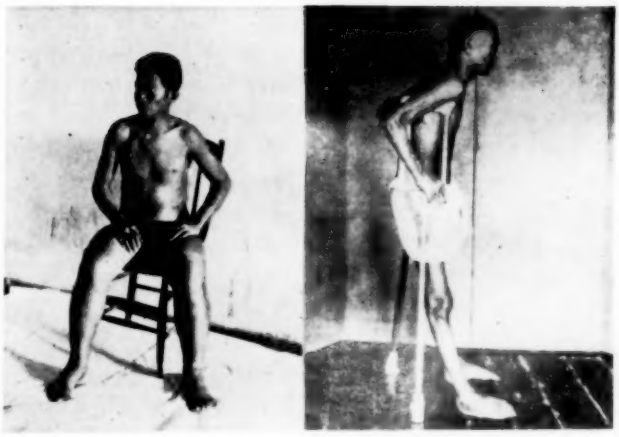

FIG. 1. "WET" BERI-BERI AND "DRY" BERI-BERI
(Herzog) (Bältz and Miura)

FIG. 2. DEFICIENCY OF ANTINEURITIC VITAMIN B. ADVANCED CASE. (Cowgill)
Photographs taken on 83rd day of subsistence on deficient diet. Notice that contracture of hind limb muscles occurs whether the animal is standing or lying down.

pensable: (1) for the metabolism of carbohydrate, protein, fat, lipoid substances and the like; (2) for the mechanisms of biochemical oxidations and reductions; (3) for immunity reactions; and (4) for the metabolism of cell nuclei. According to Dutcher (1920) the body's hormone supply may be dependent upon the vitamin content of food. This very brief summary indicates in some measure at least how broad a field the study of vitamin physiology has come to be.

It is obvious that in the short time available, one cannot give any detailed and complete review of the many deficiency conditions now recognized. A survey of the literature indicates vitamin B to have initiated more diverse lines of investigation and theorizing in regard to its function than is the case with any other member of the vitamin group. For this reason, and because of the interest which these different types of investigation possess, this dietary factor has been selected as a focus for the present discussion.

Vitamin B

What has hitherto been called vitamin B has quite recently been shown to consist of at least two physiologically active substances: one destroyed at high temperatures and effective in preventing and curing the neuritic symptoms of experimental beri-beri; the other component stable toward heat, required along with the anti-neuritic factor in promoting growth, and probably effective in curing and preventing the development of pellagra. Many workers have called this second factor the "growth-promoting" fraction of vitamin B. This is incorrect for experiment has shown that growth can occur only when both of these factors are present (see Smith, 1928).

Continued subsistence on a diet adequate except for vitamin B eventually leads to a partial or complete anorexia for the experimental ration. In the illustrative chart—figure 3—the maximum black ordinate column represents the amount of the vitamin deficient ration offered daily to the animal. The heights of the columns from day to day indicate the amount of the ration voluntarily consumed by the dog. It will be noticed that this animal—dog 39—developed anorexia

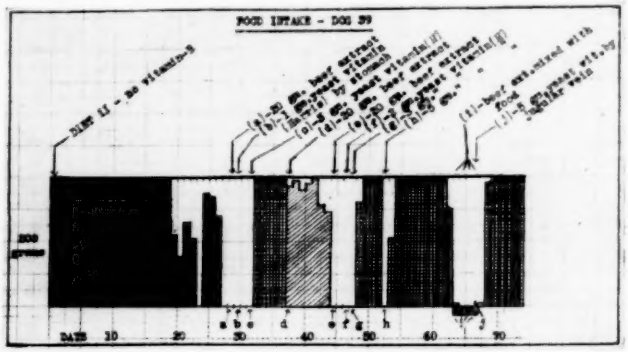

Fig. 3. (From Cowgill, Denel and Guidle, 1925).

after a period. Administration of material lacking vitamin B—in this case beef extract—did not restore the appetite for this food mixture. See letters *a*, *d* and *e*. The anorexia was corrected when sufficient amount of vitamin—containing material was given—points *c*, *g*, *h* and *j*. In each case except at *i* and *j*, the test materials were given by stomach tube in order to avoid any possible effect due to change in the taste of the ration. At *i* the beef extract was mixed with the food but the animal refused the mixture absolutely. At *j* the yeast vitamin concentrate was given intravenously. After a latent period of one day the appetite was restored. It is not possible as yet to say definitely which of the B factors is primarily involved here. Unpublished data from our laboratory suggest the antineuritic vitamin as the etiologic substance.

Subsistence on a diet lacking vitamin B may result in the appearance of characteristic skin lesions suggestive of decubital ulcers (Cowgill, Stucky and Rose, 1929). See figure 4. The evidence at hand is inconclusive as to which of the vitamin B components is required in order to prevent these lesions.

Dogs restricted to a diet deficient in vitamin B suffer an impairment of their natural immunity toward infection with *Bacillus Welchii* (Rose, 1928). This phenomenon has not as yet been traced to one or the other of the two factors contained in the vitamin B complex.

Many of the ideas concerning the function of vitamin B were advanced when the plural nature of this factor was not appreciated. Therefore many phases of the general problem require reinvestigation.

One of the first suggestions with regard to vitamin B function was that this substance is required for normal metabolism of carbohydrates (Funk, 1914). Diets rich in carbohydrates in contrast to other rations were considered to cause earlier appearance of the neuromuscular symptoms and to ren-

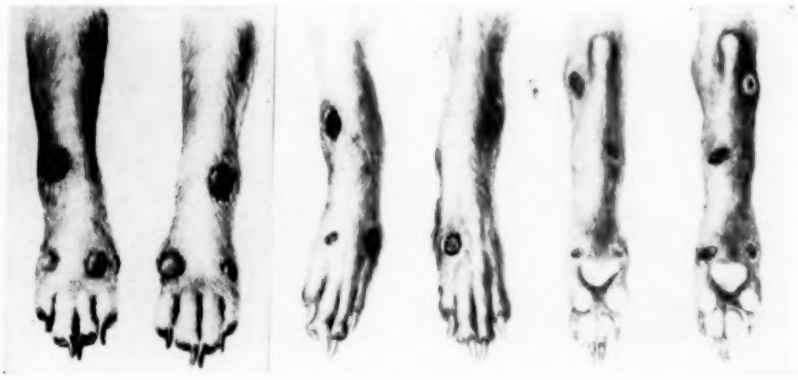

FIG. 4. DEFICIENCY OF VITAMIN B COMPLEX: CHARACTERISTIC SKIN LESIONS. (Cowgill, Stucky and Rose)

Preulcerative stage (Dog 56) — *Fully developed lesions* (Dog 55)

der the symptoms more severe. Randoin and Simonnet (1924) quite recently reemphasize this view. However, the variation in time of onset and severity of symptoms which groups of experimental animals show, is in our opinion so wide that one may seriously question any hypothesis resting largely on such evidence. The failure of Osborne and Mendel (1922) and Sherman and Gloy (1927) to observe any differences in vitamin B requirement of animals subsisting on diets having extremely unusual proportions of organic nutrients has been cited as evidence against this theory. Evans and Lepkovsky (1928) have just reported that fat in the diet spares vitamin B. A definite amount of the B factor in the form of yeast was insufficient for rats subsisting on a diet extremely rich in protein. When the ration was changed to include a fairly large proportion of fat, this same amount of vitamin B now proved adequate. Studies of the respiratory quotient in this deficiency have yielded conflicting results.

The old idea that toxins are responsible for the neuritic symptoms of vitamin B deficiency was considered incompatible with the vitamin theory and rightly so because the toxins were regarded as existing preformed in the food. A later suggestion is that the hypothetical toxins may be abnormal intermediary metabolites arising in the course of faulty carbohydrate metabolism because of absence of the vitamin factor (Walshe, 1918). The almost miraculous recoveries from the severe neuromuscular symptoms of advanced vitamin B deficiency that animals show when given the missing factor are difficult to explain on the basis of mere neutralization of toxins by the vitamin. (Figure 5.) Dogs exhibiting clonic, spasms, when handled, have been given complete relief within as short a period as four hours by intravenous injection of a suitable vitamin B concentrate (Cowgill, 1923). (Figure 7.) This is comparable to the well-known remarkable recoveries that pigeons make in similar experiments (Funk, 1914).

Attempts to show that vitamin B plays a rôle in the mechanisms of tissue oxidations and reductions have yielded diametrically opposite results (Abderhalden and Wertheimer, 1921; Drummond and Marrian, 1926).

FIG. 5. DEFICIENCY OF ANTINEURITIC VITAMIN B. ADVANCED CASE. (Funk)
Before treatment and 3 *hours after* receiving 4 mg. of yeast vitamin concentrate parenterally.

The decrease in the basal metabolic rate of animals restricted to a diet lacking vitamin B has been emphasized by many writers with the implication that the vitamin-lack exerts a peculiar specific effect on the basal rate. Most of the observations have been made on pigeons subsisting on a diet of white rice. Such a ration is deficient in several respects. Deuel and Weiss (1924), however, using the animal calorimeter at Cornell Medical College, made direct measurements on dogs subsisting on diets similar to that fed the animal shown in figures 6 and 7. The observed lowering of the basal metabolic rate was believed to be entirely accounted for by the accompanying partial starvation resulting from the anorexia induced by the vitamin de-

FIG. 6. DEFICIENCY OF ANTINEURITIC VITAMIN B. ADVANCED CASE. (Cowgill)
Before treatment. Contracture of leg muscles. Clonic spasms when handled. 18 *hours after* receiving tomato juice via stomach tube. "Steppage" gait.

FIG. 7. DEFICIENCY OF ANTINEURITIC VITAMIN B. ADVANCED CASE. (Cowgill)
Before treatment and 4 *hours after* receiving vitamin B extract intravenously: dog is now able to walk but with a slight spasticity of the hind limbs.

ficiency. Lusk concurred in this opinion.

Vitamin B has also been regarded as a specific stimulant of digestive glands like the drug pilocarpine for example (Uhlmann, 1918). We have failed utterly to confirm this experimentally (Cowgill and Mendel, 1921). The anorexia characteristic of lack of this dietary essential suggests a disturbance of gastric motility, perhaps a disappearance of the so-called hunger contractions. We have studied this problem in dogs (Cowgill, Deuel, Plummer and Messer, 1926). Only minor changes occur in the motility of the empty stomach during the early stages of vitamin B deficiency and these are insufficient to account for the anorexia. Gastric atony is almost invariably part of the syndrome of an advanced case of this deficiency.

This conclusion has been questioned (Smith, 1927) but a renewed and more extended investigation in our laboratory has only served to confirm our earlier findings (Stucky, Rose and Cowgill, 1928). Some evidence has been offered suggesting that the processes of gastric secretion are depressed in this deficiency (Farnum, 1926); also that the motility of the intestine is impaired (Plummer, 1927). We are of the opinion that the gastro-intestinal features of this deficiency are not the result of a peculiar specific relation of this vitamin to functions of the organs of the ailmentary canal, but rather are reflections of a deranged systemic condition.

The view that the antineuritic vitamin B plays a rôle in the metabolism of cell nuclei and is therefore a substance required by nearly all cells of the body has much to commend it (McCarrison, 1919; Findlay, 1921). Various tissues appear to rank in content of this vitamin according to their richness in cell nuclei; liver, kidney, brain in contrast to muscle for example. Furthermore the numerous attempts of biochemists to isolate this vitamin suggest that it is a substance closely related to well-known constituents of nucleic acid (see Krause and McCollum, 1929). Recent quantitative studies made in our laboratory of the vitamin B requirements of different size individuals of several species find a reasonable interpretation in terms of this hypothesis. If it may be assumed that deficiency of the antineuritic vitamin B is a species of nuclear starvation in which the heart and central nervous system are spared as long as possible at the expense of other organs, then the pathologic, physiologic and metabolic findings seem to harmonize fairly well. It is unnecessary to postulate, as Cramer (1923) has done, a special rôle for vitamin B in the functioning of lymphoid tissue, a tissue rich in cell nuclei, be it remembered. To do so is to emphasize but a single detail of the picture.

Vitamin A

The exact chemical nature of this dietary essential is still unknown. Takahashi's (1924) claim to have isolated this vitamin has been disputed by Drummond, Channon and Coward (1925). The data submitted by all of these investigators suggest that vitamin A is a complex unsaturated higher alcohol or a closely allied substance.

This dietary factor is required for growth. Shortage of vitamin A dur-

ing the early stages of development may have a deleterious effect for long periods (Sherman and Burtis, 1928). Translating the studies on rats to the

FIG. 8. VITAMIN A AND GROWTH.

Two rats, of same age, fed same ration except that the rat on *right* received Vit. A in addition. (McCollum).

human species, Sherman and Burtis estimate that inadequate supply of vitamin A to an infant during the first two years of life may predispose that child to infections, pulmonary disorders and the like for the following eight or ten years. This vitamin is also required for maintenance of the adult, and inadequacies of supply adversely affect longevity (Sherman and Macleod, 1925).

A characteristic eye disease develops in vitamin A deficiency. This has been observed in experimental animals and in human infants. (Osborne and Mendel, 1921; Steenbock, Nelson and Hart, 1921; Bloch, 1924).

According to Wolbach and Howe (1925), the pathological change of note is a keratinization of epithelial tissues. The infections occurring, when vitamin A is lacking, are probably of secondary origin resulting conceivably from an impairment of the cells of the protective surfaces involved. Opsonins are not decreased in

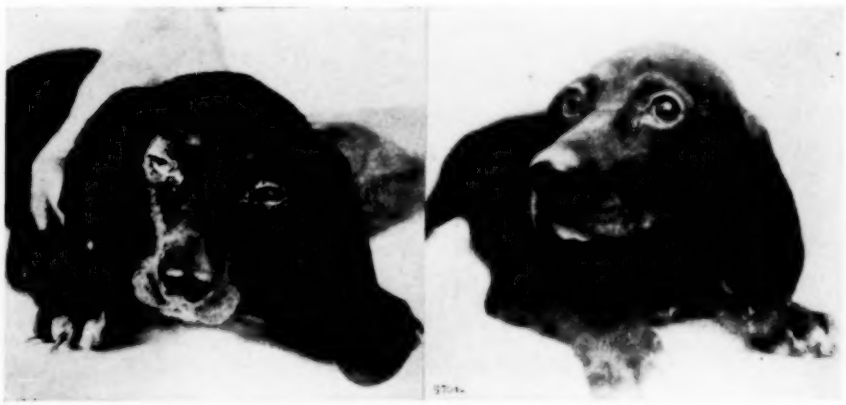

FIG. 9. OPHTHALMIA IN DOG—VITAMIN A DEFICIENCY.

Left: before treatment. *Right*: cured in ten days by addition to diet of 20 cc. of cod-liver oil daily.

(Steenbock, Nelson and Hart)

this deficiency (Findlay and Mackenzie, 1922).

It is conceivable that vitamin A plays an essential rôle in lipoid metabolism, or that it is a necessary constituent of the lipoidal membrane of cells; that in its absence, permeability of that membrane is impaired, and the cell's capacity for absorbing nutrients or discharging secretion through that membrane is lowered or destroyed. Attempts to construct anything like a detailed hypothesis concerning vitamin A function must, in view of the present state of knowledge, involve considerable speculation.

Vitamin D

When evidence was obtained suggesting that a fat-soluble organic factor plays a rôle in preventing and curing rickets, vitamin A was thought to

Fig. 10. Terrier with rickets. (Mellanby)

be that substance (Mellanby, 1919). McCollum and associates (1925) succeeded in demonstrating that the antirachitic factor is separate and distinct from vitamin A. From the recent work of Hess, Windaus (1927), Rosenheim and Webster (1926), it appears highly probable that the antirachitic factor is a derivative of ergosterol produced by exposure of this substance to radiant energy of wavelengths found in the ultra-violet zone.

The well-known facts concerning the rôle of this substance in the etiology and cure of rickets need not be reviewed here. Interesting problems now commanding attention concern the mechanism by which this factor exerts its influence on calcium and phosphorus metabolism, and its possible relation to the parathyroid hormone. Injections of irradiated ergosterol into normal animals can increase the level of blood calcium even when this element is absent from the intestinal lumen (Hess, Weinstock and Rivkin, 1928). Evidently such a rise in blood calcium cannot be attributed to increased absorption of lime from the alimentary canal. Administration of irradiated ergosterol to parathyroidectomized individuals does not produce a rise in blood calcium. Whereas the fresh egg contains large amounts of the antirachitic factor, the tissues of the newly hatched chick are devoid of it. Fish eggs and fresh fry exhibit the same phenomenon (Hess, 1929). Evidently, like vitamin B, the antirachitic factor is consumed in metabolism and the supply must therefore be renewed through the medium of food or exposure of the organism to radiant energy of the proper wavelength. Such exposure produces synthesis of this factor within the organism itself.

Vitamin C

The water-soluble factor required in order to prevent scurvy in man, monkey and guinea pig, is a substance very sensitive to oxidation, and apparently of molecular complexity comparable to that of a six-carbon-atom sugar (Connell and Zilva, 1924). Its exact chemical nature is as yet unknown. Apparently this substance plays an important rôle in the matrix of connective tissue. What the details of that rôle may be, one can only speculate upon. Not all species require this factor in the food. Scurvy has never been produced in the dog, rat or chicken. The most acceptable explanation of this fact at the present time seems to be that these species have the power of synthesizing vitamin C.

Vitamin E

In vitamin E deficiency the characteristic phenomenon observed in the female is *fetal death and absorption*. In the rat, whose gestation period is twenty-one days, this occurs at some time between the twelfth and the twentieth day of gestation (Evans 1925). In the male, lack of this factor results after a time in destruction of the germ cells and eventually the entire seminiferous epithelium (Mason, 1926). In the case of the female there is no degeneration of germ cells; the ovary and ovulation continue unimpaired throughout life.

The chemical structure of vitamin E still remains unelucidated in spite of much research. This substance is remarkably stable toward heat, light, air and many of the ordinary chemical reactions. The viscous oil obtained by Evans and associates (1925) "contains only a trace of ash, and no nitrogen, sulphur, phosphorus or halogen". Apparently it is a saturated compound in contrast to the other fat-soluble vitamins A and D.

Studies of these many deficiencies give new content to the idea expressed in the term *diathesis*. What seems to be a constitutional predisposition toward certain disease conditions may after all be the response of the organism to a deficient diet.

There has developed a tendency on the part of investigators generally to interpret all unexplained nutritional phenomena in terms of the vitamin theory. The pendulum of interest must not be allowed to swing too far away from consideration of calories, proteins and mineral nutrients, still necessary components of an adequate diet. Also one must not forget the need for a proper balance of the essential constituents of the diet already known.

A vitamin may be regarded as any substance (1) required by the body, (2) consumed in metabolic processes, and (3) necessarily provided from without because it cannot be synthesized within the organism except, as in the case of vitamin D, under special conditions. It is not unreasonable to suppose that additions will be made to the list of vitamins. The great complexity of the animal body, the variety of chemical compounds found therein, and the possibilities and limitations of the organism with respect to the processes of intermediary metabolism all afford an adequate basis for this belief.

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The Treatment of Angina Pectoris*

By Harlow Brooks, *New York City*

Angina pectoris is not a disease, but a symptom complex. It has a widely varied etiological pathology which produces, nonetheless, a symptomatic picture of very striking and significant character, best as first described by Heberden in 1768.

The pathology, basically concerned is the cause of death in angina pectoris. All or any of these lesions may exist without the appearance of the symptom complex and the pathological changes are in themselves probably quite as likely to cause sudden or ultimate death without angina as with it. The symptoms of angina in themselves are not lethal, they may probably exist or at least be very closely simulated without any danger of sudden death. Symptoms are only dangerous when associated with or incited by the basic pathology of the condition.

The pathology of true or sinister angina pectoris is disease of the coronary arteries, aortitis, myocarditis or myocardial degeneration. In some instances pericarditis about the cardiac base may also so act, but it is also then commonly associated with disease of the heart muscle.

Relief or cure of the basic lesions, cures and eliminates the complex. Relief or cure of the symptoms does not either remove the disease or materially alter its dangers. The symptoms are produced by a sensitized nervous arc, having its basis in stimuli which originate from the primary cardiac disease. Breaking of this arc, as, for example, by sympathectomy may entirely relieve the symptoms, but it has little or no influence on the basic pathology or on the inherent danger to life.

The speaker feels that the recognition of these axioms is essential for a proper and adequate understanding of the treatment of angina pectoris.

It has been noted that the basic pathology of angina pectoris consists exclusively of cardiovascular lesions. The dominant hereditary influence existent in most diseases of this character is apparent to every thoughtful practitioner.

Every one of us can call to mind families in his clientele which are particularly prone to arteriosclerotic disease, to hypertension, to cardiac fibrosis, to death from cerebral vascular insult, and most of us know also families in which angina pectoris is so frequent an occurrence as to correctly justify the appellation of Anginal Families.

Such being the case, the speaker feels that much can and should be done in the way of prophylactic treatment in such families so that this

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group tendency is eliminated or minimized.

Families which show a tendency in this direction associated with obesity, for example, may largely lessen this trend by careful study and control of the dietetic and physical activities of its younger members. We must of course recognize that we can not entirely control these tendencies, for many of them are founded on endocrine dyscrasias, still even these influences may be to some extent controlled or prevented in early youth by study and treatment directed to the thyroid, pituitary and perhaps to the sexual glands.

Physical exercise control is a very important matter in the development of the youths of such families. Much danger lies in over exercise and in the cultivation of cardiac hypertrophy, arterial tension, and the like, from over physical exertion in early life. The youth of an anginal family should not undertake football, the crew, or the long distance run in his school and college years. On the other hand adequate physical exercise beginning in early life and continuing in temperance into the adult period is to be encouraged and directed. Excesses must never be permitted. Walking, golf, swimming, horseback riding and the like never in excess, are always beneficial, unless inherent heart defects are known to exist.

In the anginal family the youth should be taught self-control, not only of his physical expression but of his mental and emotional life also, for we all recognize the tremendous rôle which emotional stresses play in the evolution of angina. A very important matter in the prophylactic treatment of angina is the development during youth, of diversions, avocations, hobbies and the like which lead to emotional rest and relaxation. Habits of healthful and adequate sleep must be also developed.

The infections, many of the juvenile types, which we all too frequently ignore, should receive more than ordinary attention in families which manifest this tendency. Temperance in all things, particularly in the use of alcohol, tobacco and of the condiments in general should be engendered.

Such infections as rheumatism, tonsillitis, recurrent bronchitis, the streptococcus infections in particular, should be promptly recognized and treated in these individuals. Influenza, especially, should be punctiliously treated even in its milder forms in these patients. Following any of the infections, especially after measles, scarlet fever, tonsillitis and bronchitis, an adequate period of rest should be enforced for full convalescence. The child should be immunized against diphtheria and typhoid fever. Adenoids and sinusitis should be promptly treated if they arise. Pyelitis in such families should not be permitted to drag itself along through long periods of neglect.

Measures of this character beyond any doubt materially lessen a family tendency toward cardiovascular disease of any character, and no more in any other than in the complex of angina pectoris.

The selection of a life occupation is another preventive matter of very great importance in anginal families. Certain occupations are manifestly unfitted by their normal requirements for

men of this hereditary taint. It is a very common experience in our technical schools to see young persons, study of whose history, previous sicknesses, and especially of the family history, would show that they lack ability to sustain the stresses of the elected vocation. Many young men are ruined for their life calling by negligence in this obvious matter. Such restrictions apply with particular pertinency to young men with a family tendency toward angina pectoris.

The growing habit in America of taking vacations is certainly a step in the right direction in the preventive treatment of angina pectoris, but in too many instances these tendencies are directed into wrong channels and become a detriment rather than a benefit. The physician may find, for example, on any golf course, men the subjects of real or tentative angina who under the delusion that they are benefiting their health, all untrained and unprepared from a physical standpoint, indulging in stresses well fitted for the young college athlete, but not for the mature and frequently overplump business or professional man who six days out of each week must sit at his desk, stand on the turbulent floor of the stock exchange, or under the tremendous responsibility of the operation theatre. Old men try to play tennis with their sons, to defeat them at hand ball, to outdistance them in swimming, to outclimb them in the mountains—many of them develop angina.

Once angina has developed in any patient the physician should make the most painstaking sort of study possible of that subject, of his heredity, past history, especially as regards the infections and of his habits and obligations. The object is to detect the cause of the basic pathology, to remove it if possible, and to limit or check its ravages before permanent and unhealable lesions have developed.

The recognition of syphilis should be practically simultaneous with its vigorous treatment. It has been frequently pointed out, by Wile, Stokes, the author and others that this preliminary treatment should not be inaugurated with the arsenicals but with mercury, bismuth and the iodides. Arsphenamin in all its forms is a dangerous agent to employ in cardiovascular syphilis until the patient has been at least once brought under the full effects of the iodides, mercury or bismuth. Most cases of angina pectoris caused by syphilis can be benefited symptomatically by specific medication in conjunction with the usual general measures. Early cases may be clinically cured and even late cases greatly benefited.

Gout is a cause of angina pectoris in at least a certain number of instances. Gout can be cured in its early phases and can be more or less benefited in all except its terminal aspects. Anti-gout treatment in gouty cases of angina pectoris will usually result in benefit and occasionally cure. Atophan, colchicine, the alkalies and, above all, dietetic treatment of gout is imperatively called for in those instances of angina in which gout is a probable etiological factor.

The rôle of rheumatic infection in the development of angina pectoris has not been sufficiently emphasized in the past. Probably more than any

other one factor, rheumatic fever in any of its protean manifestations is the most frequent cause of the fibroid heart. There can no longer be any question but that fibrosis of the heart muscle is a frequent basic pathology of the symptomatic picture of angina pectoris. Early, vigorous and persistent treatment of rheumatism is beyond question at least deterrent of the development of these cardiac changes. Particularly important is the adequate recognition in these instances of necessary slow convalescence and of aggressive convalescent treatment in cases in which the heart is known to be involved. The salicylates are beyond question both protective and curative in these instances and their employment in chronic and recurrent cases is very highly beneficial not only in the prevention of angina pectoris, but occasionally also in its mitigation and relief. The value of the iodides also in those cases originating from myocardial defects is an established clinical fact. This is illustrated even in occasional cases of active angina in which the iodides and less frequently the salicylates give decided relief of the complex.

As a further illustration of the need for specific treatment in angina pectoris one may cite those cases which appear in diphtheria. I have seen but a single case however in which the administration of diphtheria anti-toxine was followed by improvement of a startling character. In this instance, as perhaps in others cited in the literature, the effect may have been rather that of a foreign proteid reaction than of a truly specific nature.

In true angina pectoris one must presuppose as a basic pathology either disease of the coronary artery, of the aorta, or of the myocardium and possible, though I believe rarely, disease of the pericardium, particularly of that portion at its application to the root of the aorta. Rest is an absolute essential in the treatment of all these lesions and so very essential is rest in the treatment of angina, both from the standpoint of relief of symptom and of improvement of causative lesion that your speaker is impelled to consider rest as one of the specific measures for the treatment of angina pectoris.

Most cases of angina pectoris benefit at least symptomatically from a period of rest in bed. In many of these cases, if not in all, rest affords a break in the habit element which plays an important part in the development of attacks and if associated with proper medical treatment it also affords a period of lessened physical and emotional stress in which reparative alterations in the essential lesion may be encompassed. Anginal attacks are, however, incited both by emotional and by physical stresses, probably no more by the one than by the other. There are instances in this disease in which confinement to bed for longer than a mere temporary period leads to such emotional stress, perhaps because of neglect of business or of other crucial obligations, that the patient is injured rather than benefited by too prolonged a period of enforced rest.

Every successful physician has seen cases of angina pectoris in which symptoms were made worse instead of

better by absolute rest treatment. Many instances have been observed by your reader in which it was found most beneficial to permit even during rest periods a certain degree of mental and physical activity. The proper determination of the degree of rest which should be utilized in the treatment of any individual case of angina then must presuppose a very intimate knowledge on the part of the physician of the character, mentality and even of the social and business requirements of the patient. Here art steps in and dominates science in the practice of medicine.

In order to be most beneficial, rest treatment must be most carefully studied and individualized. Shall or shall not the patient receive the privileges of the bathroom, must he use a bed pan, or may he use a commode? These are important matters which may only be determined by intimate knowledge of the patient, rather more than of the disease, oftentimes.

The time and manner of the resumption of relatively normal life habits after the period of rest treatment is a very important and difficult problem. Only close observation of the results in each special case can really determine this. Most cases sooner or later must resume at least an ambulatory invalidism, and in most instances it is far better and wiser that they should do so. Your reader has never seen a case of angina pectoris eradicated by rest treatment, no matter how long enforced. Angina pectoris occurs at a period of life when degenerative changes in the circulatory mechanism are naturally progressive. Too much rest, too little circulatory demand may tend to augment the rapidity of this process. All this must rest on the judgment of the individual case. There is perhaps, no more severe test of understanding and real knowledge of medical art than is required in such cases.

In very many cases rest of a merely physical character must be augmented by the use of drugs. Those most suitable for the particular case are largely determined by the patient himself. In instances of hypertension, the bromides, chloral and similar sedatives are most useful, but where, as is so frequently the case, hypotension instead of hypertension is present,, these drugs which have a hypotensive action are not well exhibited, and we turn more naturally to the opium group of drugs. They are imperative in some cases, especially those in which a coronary thrombosis has taken place. There is another drug of the sedative class which has long been recognized as of essential benefit in these cases. Of it Heberden said: "Quiet, warmth and spiritous liquors help to restore patients who are nearly exhausted, and to dispel the effects of a fit which does not soon go off." It is very possible also that the euphoristic effects of the alcoholics play a beneficial role in cases of angina pectoris, but anyway your speaker is convinced that we possess in properly chosen alcoholics a very efficient weapon for the combating of angina pectoris, especially in that of the late adult and in old age.

Healthy normal sleep in abundance is the highest index of rest treatment in angina pectoris. It is essential in any phase or condition of the complex

and it must be obtained by any means possible, preferably without drugs, but if necessary with their assistance.

The last few years have furnished us with a group of drugs which are of such direct action in angina pectoris, especially on the basic lesions of the complex that we may almost consider them in the nature of specifics. Your reader is not universally enthusiastic over these drugs, he has not felt that they have lived as yet fully up to the hope which the pharmacologist and particularly the foreign drug manufacturer have promised, but they are definitely valuable in many cases. They are those drugs which act, as pharmacologists affirm, through specific dilatation of the coronary vessels and possibly otherwise to improve the circulation within the heart muscle. Mostly they are modifications or adaptations of caffeine or theine. They are euphalline, theocalcine and the like. Their efficiency brings to mind that before recent days coffee and tea were employed by our predecessors in the treatment of angina pectoris as in other forms of cardiac disease. Nowadays, as your reader believes, largely through the advertising activities of substituted materials they have fallen into disrepute in the management of cases of cardiac disease.

We must not neglect the subject of the nitrites and of the very large group of vasodilators in the treatment of cases of angina pectoris. Their almost indispensable character in the management of the acute attack has in some instances blinded us as to their essential value as preventives of the attack or as medical agents in the routine treatment of cases between the attacks. These drugs through their ability to dilate and relax the arterioles may be used to excellent effect in many instances of the disease in its quiescent phases. While this is particularly true of those instances in which hypertension and arterial spasm are elementally present they often act well in the prevention of the paroxysm in cases of normal or even in hypotension. Your reader has found them particularly valuable when given at bedtime especially in those cases which develop attacks during sleep. As a rule the reader has found sodium nitrite and erythrol tetranitrate most efficient in this respect because of their slower and more prolonged effect apparently, but nitroglycerine and amylnitrite are also useful for this purpose. Benzyl benzoate is beneficial in this usage also, probably much more so than in any other phase of the complex.

Probably the sedatives, chloral hydrate, the bromides, luminal and the like, though chiefly mere sedatives, also act in this manner in some degree. They are all useful and which is the most beneficial in any instance can be determined only by clinical experiment in the individual case.

Certain instances of angina pectoris appear to be incited by a lack of sufficient cardiac tone, perhaps by failures in conductivity. Your speaker refers now of course to those cases which are based on a pathology of myocardial defect. In these digitalis and digitalis-like drugs act beneficially. It is the impression of your reader that in most cases of angina which originate from coronary or aortic pathology that the digitalis group of

drugs tends to make the symptomatology worse rather than better, but in those of myocardial origin, they often benefit just as sometimes we are forced to use digitalis after coronary thrombosis, contraindicated in this circumstances as it usually is. Caffeine also seems to act very beneficially in certain of these cases. It should never be pushed to the point of mental excitement. Strychnia also has its indications, as your reader believes, in those cases in which extensive myocardial lesions have resulted in a depressed muscle irritability.

Too much has probably been written on diet in angina pectoris. It is rarely of real importance. There is no diet for the condition any more than there is a specific drug treatment for all cases. We must recall again that we are not treating a disease, but an individual, with an extremely varied pathology which chanced to produce a symptomatology which happens to present a very striking and apparently characteristic picture. The individual with the complex may require a diet or may not, but there is no suitable dietary for the complex as such.

It has already been said that cases the subject of gout will require an antigout diet, cases the subject of grave anaemia will deserve a diet rich in iron. Obese patients as a rule will do best on a diet low in starch and fat, malnourished patients improve on a pushed general diet, and so on. Again the fact must be determined from a full consideration of the probable basic pathology and from a study of the results which follow application of these conclusions. It is a matter of clinical experiment which is quite as scientific and infinitely more important than studies with the lower animals.

It is a commonly recognized fact that many paroxysms of angina are excited by gastric irritation or distention, by intestinal flatulence, or even by such definite irritative gastrointestinal lesions, as duodenal ulcer, chronic appendicitis, colitis and the like. Gall bladder disease is not only often closely simulated by angina pectoris, but it may also beyond doubt precipitate the paroxysm in some instances. It is obvious then that the diet problem may very rarely become of extreme importance and one may well recommend in generality that all those foods which produce difficulties of digestion, either chemical or mechanical, may be wisely eliminated.

As has been previously intimated, the writer feels that the alcoholics properly used benefit rather than otherwise. This is especially true in late adult life or in old age. The use must not be confused with the abuse of alcohol, however, and the determination as to the benefit of alcohol in any given case depends on clinical study as definitely as is the case with any other agent utilized in the disease. Wine or beer with dinner, or a highball just before retiring will not infrequently ward off attacks or much mitigate their severity.

Tobacco has been generally condemned for usage in cases of angina pectoris. The reader is one of those who believes that there is a very distinct demarcation between tobacco angina and true angina, nor does he feel that tobacco alone is ever capable of causing the lesions essential to the development of true lethal angina pec-

toris. Nevertheless he is convinced that tobacco in truly anginal cases increases the severity and occurrence of the attacks. It should be forbidden in practically all instances of the complex.

The surgical treatment of angina pectoris has received very much attention within the past few years. From a perusal of the surgical literature on the subject one is almost invariably regretful that so little conception of the essential pathology of the complex has backed surgical research and one notes almost invariably that relief of the symptoms is considered as a cure. Surgery has, nonetheless, established for itself a definite place in the treatment of angina pectoris. It is definitely and only indicated in those cases in which the severity and frequency of the paroxysm is great and in which medical management and treatment has served neither to relieve the pathology or to control the symptoms. There is still another essential qualification which the internist must consider before he turns the case over for surgical treatment. The suffering in these cases must be of a very severe, well nigh unbearable character, not relieved or rendered tolerable by medical management.

Surgery at the best but breaks the connection between the essential lesion, which is capable of causing death and which must remain as dangerous as ever after the operation as before and the symptom-producing mechanism which produces the clinical syndrome. This is all that may be accomplished by surgery, and it is quite enough to justify it in a good many intractable instances where suffering has rendered life a mere agony and unwarranted burden. As Mackenzie prominently pointed out, the removal of the symptom or safeguard of pain and suffering probably in some degree lessens the chances of life for the patient because it eliminates the warning of the attack when the patient undertakes things which induce the complex.

Very briefly surgery in angina pectoris consists in the removal of the sympathetic ganglia or resection of the sympathetic trunks in such a manner as to block the disease impulse originating in the cardiac lesion from demonstration or appreciation through the sympathetic chain. This may be successfully accomplished in the hands of a skilled surgeon in a considerable percentage of cases. No change in prognosis is accomplished but relief from agony is well worth while in some instances.

Injection of the nerve trunks has been recommended and successfully performed by Swetlow, Schwartz and others. It acts in the same manner, though possibly in a less permanent way as the surgical procedure just mentioned. The method, although alleged to be simple, probably requires quite as high a technical skill as does any of the surgical operations. It has the same disadvantages as more overt surgery and is probably less likely to produce permanently good symptomatic result. It has a field in those instances which deserve surgery for the relief of suffering and which refuse it because of its name.

Most of the reader's time has been devoted to general treatment of angina pectoris for the reason that many

practitioners fail to realize what may be accomplished in the way of actual cure and amelioration of the complex. Little time now remains in which to consider the treatment of the paroxysm. This does not express your reader's judgment of proportions but rather the obligations of the programme. Further also the reader feels that the average practitioner is already well conversant with the matter of treatment of the immediate attacks, and there is therefore little on which your reader may instruct him.

The attack should be stopped as promptly as possible, not only because of the intense suffering which it frequently entails, but also because there can be no doubt but that attacks which are permitted to mature unquestionably tend to increase the frequency of future attacks, that is, it tends to the establishment of a habit of attacks. Even mild attacks should then receive attention, death is almost as likely to occur in mild attacks as in severe ones, but the longer the attack the more lethal it is. Hence the physician should instruct his patient to check the slight attacks and not to allow them to develop into severe ones.

Whenever the patent is seized, he should immediately stop whatever he is doing. He should assume as nearly as possible a position of rest. In many instances this alone will suffice to abort the attack. In case prompt relief is not afforded the patient should take or be given nitroglycerine in the form of the spirits of glonoin, as a tested tablet, preferably hypodermic of nitroglycerine, either swallowed with water, or given hypodermically, or given intravenously if a physician is at hand. There is no advantage gained from retaining the tablet in the mouth until it dissolves. Some cases react perfectly to the fumes of amyl nitrite inhaled from a crushed pearl or ampoul of the drug with which he should always be provided in these cases.

If prompt relief is not afforded, the dose should be repeated, if necessary, several times. The patient should be always fully instructed as to the effects of the drug, otherwise he may be seriously frightened by its effects. A little experiment will soon demonstrate which drug and which form of it is most useful in any individual case, but it is well for the patient to be provided with both nitroglycerine and amyl nitrite in preparation for a prolonged attack without medical assistance being available.

Where the attack still persists in spite of the adequate use of the nitrites, morphine should be given, it is the drug of all others which is most universally beneficial and it may be required in very large dosage, one half grain at a dose, repeated several times if need be. Patients of strength of character who are not likely to abuse or misuse morphine, after having been fully instructed as to its indications, danger of its frequent use and the like, may be furnished with sterile hypodermic units of morphine, especially if the requirements of their life obligate their being distant from probable medical assistance in case of an attack.

The patient should not be moved until the attack has subsided. There is good reason to believe that as the attack subsides its danger also diminishes proportionately.

Self treatment is in general a very unwise thing on which to instruct a patient, especially a neurotic and emotional type, but this is a condition in which self instruction and self treatment must usually be utilized if the full and most beneficial effect is to be realized. It goes without saying that if the attack does not quickly subside or if it is soon repeated a physician should be sent for, but most intelligent patients soon learn how to care for ordinary attacks themselves if they receive adequate instruction from their physicians at the outset.

Where attacks persist in spite of treatment or when they recur, coronary thrombosis of some extent has usually taken place, this requires persistent and careful treatment which should extend over days or even months. This is obviously a subject beyond our consideration in this crowded program.

The Coronary Problem*

By Arthur R. Elliott, *Chicago, Illinois*

Coronary arterial disease presents a varied clinical picture. The abundant literature which has accumulated since Herrick's forceful and illuminating description of coronary occlusion in 1912 seems to be mainly devoted to certain of the more dramatic aspects of coronary disease, notably angina pectoris and coronary thrombosis with its consequences. This brief discussion will be concerned with coronary manifestations that are less frank and typical than the major developments referred to, in short with what has been termed because of this obscurity, "occult coronary diseases."

Outspoken sensory complaints, such as angina pectoris, may not develop from disease of the coronaries, for all grades of sclerosis and all degrees of occlusion even to obstruction of one or both main trunks have been found at necropsy in individuals who had never experienced angina. Willius and Brown in 1924 undertook an analysis of 86 autopsies, representing unselected proved cases of coronary sclerosis, for the purpose of determining the frequency of occult coronary disease. The result of this research was their conclusion that 34 of these cases or 40 per cent might fairly be classified as occult, inasmuch as diagnosis had not been possible during life because of insufficient subjective and objective evidence. Morawitz and Hochrein recently reported one year's experience which comprised 137 autopsies where essential changes of the myocardium and coronary arteries were present. They found 91 showing extensive coronary sclerosis and of these 91 patients 75 per cent had not complained of subjective symptoms of heart disease. Without further citations from the literature we may accept the fact as proven that coronary pathology of sufficient extent and degree to bring about cardiac death may exist without attracting attention by unequivocal signs and symptoms. There is really nothing surprising about this considering the fact that vascular degeneration is the main-traveled road to old age and that some degree of atheroma of the aorta and its proximal branches is one of the almost inevitable liabilities of maturity. It is notorious that aside from the aorta, the coronary arterial circuit is more frequently the seat of disease than any other in the body. These arteries, first and most important divisions of the aorta, receive as it were at first hand the buffetings borne by the parent stem and share in large

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measure the ill effects of a lifetime's strains and stresses. Walkoff is credited by Riesman with the statement that the thickening of the intima of the coronary arteries surpasses that found in other arteries at the same age, and the statement is current (Werley) that these vessels are sclerosed twice as often as the arteries of the brain and three times as frequently as the arteries of the kidneys. Moreover, the coronaries may be found diseased while all other accessible parts of the vascular system appear unaffected. Attempts to explain this peculiar susceptibility to damage have been unsatisfactory and we will not discuss the question here further than to comment that the obvious explanation remains the most plausible, namely, their immediate geographical relationship and intimate dynamic copartnership with the aorta.

The heart muscle because of its continuity of function must it would seem be particularly sensitive to changes in its blood supply. This appears to have received convincing proof from experimental investigation and it is well known clinically that disease of the coronary arteries is one of the most important causes of myocardial weakness. Unfortunately for the interests of clinical clarity it appears impossible to estimate with any degree of certainty either from the amount of functional disturbance or symptomatic discomfort the extent of involvement of these vessels. In one case we see death result in a paroxysm of angina or from the syndrome which we have come to recognize as coronary occlusion without there having occurred any clinical manifestations of significant character and with a minimum of arterial pathology at necropsy. In the next case it may be there is revealed the most extensive obliterative processes without any great abridgement of the patient's activity or comfort and even large infarctions and parietal aneurysms resulting therefrom have been known to develop painlessly. Osler long ago asserted that a man might get along very comfortably although with a lowered range of efficiency upon one-fourth of his normal coronary blood supply. It seems a fair assumption that the factor of safety under such circumstances is the vascular reserve that is built up as age advances by means of new anastomatic connections within the coronary circuit and between those vessels and surrounding neighborhood arteries with some help doubtless from the Thebesian vessels. This point granted, an inference similarly drawn is that the later in life coronary obliterative developments are postponed the better tolerated they are. This indeed appears to be the case and there is testimony from many sources that the prognosis in coronary obstruction stands in a rough manner in inverse ratio to the age of the patient. An added reason for this may arise from the greater cardiac overload carried in early middle life and the greater importance of syphilis in that age group. In the sixth and seventh decades life has taken on a more leisurely pace and syphilis as a factor fades into insignificance.

The only diagnostic criteria which at present appear available for the certain recognition of coronary disease are on the clinical side, the occurrence

of angina pectoris and the development of coronary occlusion, while on the laboratory side there are certain changes in the electrocardiogram indicating more or less severe muscle damage. If we insist upon these requirements before venturing a diagnosis most of our coronary cases would escape classification. On the other hand, one may doubt whether we should espouse such liberal views as those recently advocated by Morawitz and Hochrein,[1] who think that we may assume with great probability the presence of coronary sclerosis clinically, if in persons of advanced age signs of heart disturbance develop, even if such are unaccompanied by pain, and that every patient of this kind is threatened with sudden death. This is equivalent to saying with a flourish of the Absolute that old age is a disease and that to the aged death is imminent. Fortunately not every old man with a skipping heart has clinically important coronary defects. Every human being who survives long enough will undoubtedly develop sclerous changes in his coronaries but these may be no more than what is going on equally in the rest of his arterial system and need not cause the heart to break pace with the body mechanism as a whole; in other words, his heart may be just as good and no better than the rest of him, and should his heart falter, so indeed may his stomach or his brain or his legs and for the same reason. In coronary disease as with defects elsewhere in the body we might perhaps draw some line of distinction between active and inactive pathology. Not every chronically infected gallbladder is a symptom-breeder calling for surgical removal and a man may carry a slowly enlarging prostate into a ripe age and to his grave without ever experiencing more than some frequency of urination. In similar manner the sexagenarian with a sclerotic heart but a reasonable mind may by moderating his pace live very comfortably and efficiently and never suffer an angina. This may be an illustration of what the philosopher had in mind when he surmised that "at forty every man is either a fool or a physician"—he either listens to the voice of experience and regulates his life according to its precepts or he goes the way of all fools —to destruction.

The concentration of medical attention upon coronary disease during recent years has resulted in stigmatizing various cardiac developments as coronary in origin which were not formerly suspected of belonging in that category. Notable among these are chronic myocarditis, the failing heart of hypertension and certain of the arrhythmias arising in the mature. It may prove a fair prediction that as time goes on intensive study of the coronary circulation in all forms of sclerotic cardiopathy will more and more accent the importance of obliterative changes in that circuit in bringing about functional decline. Invariable and careful exploraton of these vessels as a routine in non-cardiac deaths among mature individuals and a careful coordination of such findings as are revealed with the clinical history may give us in time a more adequate understanding of the problem.

We have come to interpret angina

[1]Morawitz and Hochrein: Munch. Med. Wchnschr., 1928, 5. 17.

pectoris as a manifestation resulting from ischemia of the myocardium. Functional overload raising the nutritive demand for the moment above the level of vascular capacity elicits the tell-tale sensory protest. This interpretation helps us to a better appreciation of the symptoms of coronary sclerosis. A liberal translation of the term "angina" is essential if we are to include the various sensory discomforts, aches, pains, constrictions, pressures, burnings, etc., according to the terms of the patient's description. Bizarre in their variety they are equally peculiar in their location—in one case in the abdomen, in another in the neck or occiput, precordium, substernum, wrist or rectum. If they have any feature in common it is their dependence on overload for their production. Effort, emotion, eating, coitus are apt to infringe the sensory well being, yet the pains may arise during sleep in the small hours of the night. To the sense of alarm which is their psychic accompaniment is often added a confusion of mind, doubling the feeling of insecurity. Even when his discomforts are mild and bearable the patient's obvious anxiety hints at a tragic feeling that they represent a factor which in the end may prove his undoing. In certain cases there may exist no painful discomforts but the heart is periodically disturbed in its rhythm either by a run of premature contractions or there may occur definite attacks of paroxysmal tachycardia. The latter development arising for the first time in middle life is an extremely suspicious circumstance. Fibrillation in hypertension or with aortic atheroma is probably more frequently than not the result of a sub-lethal coronary occlusion. In the sclerotic cardiopath any abrupt change for the worse in circulatory efficiency should be distrusted as probably the result of coronary obstruction even if no pain precede or accompany the transition. It will be agreed by experienced clinicians that a great deal of difficulty may be encountered in the satisfactory interpretation of sensory discomforts that are presumably anginal. If they are located in the upper abdomen differentiation from gall-bladder, gastric or duodenal disease may be difficult. If in the chest other structures than the heart may be to blame and the so-called radicular syndrome calls for attention. How difficult the solution of the diagnostic problem may prove is illustrated by the following case at present under observation.

On the first day of the present year there was referred to us for examination a successful business man of the high pressure type. He gave his age as 52 and related the following history: At the age of 30 he had had a severe attack of migratory febrile arthritis without visceral complications. For many years he had been an occasional intemperate user of alcohol and was always a heavy smoker of cigarettes. When 49 years of age he passed a kidney stone, was cystoscoped and infected and his urine has ever since contained pus. One year before consultation toward the end of a period of unusual business strain he suddenly experienced a burning pain in his epigastrium with rapid fluttering action of the heart and dyspnoea. He presently broke into a profuse perspiration and with that the attack passed off

leaving him strangely exhausted. Two months later this experience was repeated rather more severely. On this occasion as before, the sensory discomfort was epigastric in location with limited radiation upward along the left border of the sternum but not into precordium, shoulder or arm. The heart fluttered and he had a desire to belch. He was dyspneic and sweat profusely. These discomforts persisted but a few minutes and left him feeling weak, anxious and depressed. Following this second attack there occurred at irregular intervals especially if he ate or drank heavily or became excited, milder discomforts somewhat similar except in degree to those described. About the middle of November he has his most severe attack. This wakened him from sleep and lasted three-quarters of an hour. He sat rigid on the side of his bed afraid to move and bathed in a cold clammy sweat. Morphine was administered by his physician. Although he had recovered satisfactorily from previous attacks, this last one left him weak and dyspneic and he had not regained his former comfort or efficiency at the date of our consultation six weeks later. Hardly a day passed in the interim that he did not experience some sensory discomfort. These were not always the same and analysis of his symptoms as described enabled one to separate pretty definitely three different kinds of disturbance. At irregular intervals he would have attacks of fluttering heart action, dyspnea and clammy perspiration with exhaustion afterward. At other times and much more frequently there would occur a sense of epigastric burning radiating upward with a desire to belch and if he succeeded in doing so relief was instant. A third complaint was of frequent vague feelings of aching and soreness in the precordium and lower left costal region. These often occurred at night and were to some extent but not always amenable to changes in position. The essential findings brought out by physical examination were an easily appreciable degree of general arterial fibrosis, a slightly enlarged heart with distant unsatisfactory tones, the pulse rapid but regular, blood pressure 130/100. There was no evidence of circulatory stasis. The prostate was smoothly symmetrical but slightly enlarged and the urine sediment contained much pus and a few casts. Here then we have a clinical history pointing clearly enough to the heart and the nature of his symptoms made it likely that he had coronary sclerosis. The varied character of his discomforts and the meagreness of the physical findings rendered the problem a very interesting one to unravel. He remained ten weeks under close observation and the upshot of the investigations may be summarized as follows:

The electrocardiograms showed low amplitude in all leads with isoelectric T wave in lead I. The amplitude improved under rest and digitalis but did not reach normal. X-ray measurements of the heart gave a cardiothoracic index of 44 per cent, the great vessels measuring 7.2 cm. with undue prominence of the aortic arch. There were revealed definite arthritic changes involving the anterior and posterior surfaces of the dorsal vertebrae especially clear about the fifth and sixth.

Gastro-intestinal barium fluoroscopy revealed nothing of importance except that there was found to be a gastric diaphragmatic hernia which measured about one and one-half inches in diameter through the esophageal hiatus of the diaphragm. Basal metabolism and blood chemistry were within normal limits and the Wasserman test was negative.

While under observation in the hospital there occurred three attacks of substernal oppression with fluttering of the heart identical in every feature with the three attacks included in the clinical history. These sensory discomforts were found to represent paroxysmal tachycardia, the rate in each instance going to 180-200. Their duration was from ten to fifteen minutes and they were accompanied by a profuse clammy sweat. Two of these paroxysms were promptly controlled and terminated by pressure on the vagus in the neck.

When this patient's sensory symptom complexes are checked against the above findings we perceive that there is a reasonable explanation for at least two of them. His attacks of epigastric burning sensation after meals relieved when he succeeds in belching may be accounted for by the presence of a small gastric herniation through the esophageal opening in the diaphragm. Release of air tension in the gas bulb of the stomach by belching brought him instant relief. We have in this mechanism a satisfactory explanation of one subdivision of his sensory disturbances which removes it outside the range of coronary effects. In similar manner, a second symptom group may be disposed of by attributing to the osteo-arthritis in the mid-dorsal spine the causation, through nerve root irritation, of the persistent soreness and pain in the precordium which was according to the patient's experience more or less constantly relieved by changes in posture.

There remains as a concentrate after thus deleting two of his three suspicious symptom groups, the paroxysmal tachycardia to be accounted for. This did not develop until the patient was fifty-one years of age, after years of excesses and hard nerve-wracking work. This fact raises at once the presumption of myocardial damage as an etiological background. Other cardiac phenomena present consisted of a persistent low pulse pressure, a decidedly equivocal electrocardiogram, rapid rate, poor heart tones and generalized arteriosclerosis. Time alone will tell how severe the encroachment is on this patient's coronary blood flow, but I feel sure it will support the conclusion that there exists serious obliterative coronary endarteritis.

Experienced internists will see in the foregoing briefly related case incomplete and unconcluded as it is, an illustration of the difficulties that this problem is constantly presenting for solution. Many times certainty of decision as to whether important coronary defects are the direct cause of complaints is for the moment impossible, the matter being left for Time to decide. Where clinical grounds are insufficient special methods of investigation, such as x-ray and electrocardiography, may decide the point. The high incidence of certain graphic abnormalities in proved cases of coronary disease makes the electrocardiogram a valuable adjunct in interpreting the clinical problem. Variations may be

revealed in the tracing that center attention at once on the coronaries and may thereby aid decisively in the identification of the occult type of coronary sclerosis. Careful clinical study with meticulous care to secure a complete and detailed history aided by routine electrocardiography furnishes the best guarantee of solving this difficult diagnostic problem.

Fatigue and Infection

By W. L. Holman, *Department of Pathology and Bacteriology, University of Toronto*

THE title of my paper, "Fatigue and Infection", will bring many different concepts to the minds of those reading it. What do you and I mean by the word "Fatigue", and what do we mean by the word "Infection?"

In a general way, we believe Sir James Paget's dictum to be true when he says, "You will find that fatigue has a larger share in the promotion or transmission of disease than any other causal condition you can name".

There are so many kinds of fatigue that our ideas are apt to be too general or too limited. Muscular fatigue comes to most of us as the best example of fatigue but we usually, even here, fail to appreciate that it is not a local or circumscribed phenomenon but a complicated condition of failure in the efficiency of the whole organization to meet the particular demand.[1] We further recognize that training delays the onset of fatigue but it is not easy to say just what this training accomplishes, or the mechanism of its production. The fundamental conception is concerned with the reactions of certain cells or groups of cells to certain kinds of stimuli. Among the innumerable stimuli to which the cells of our body respond are those arising from the presence of microbes. Such stimuli often demand reactions in cells with other specialized functions, and the failure to adequately respond may be due to many factors such as previous over-activity or under-activity, interference with blood supply, faulty diet and similar general nutritional deficiencies.

However difficult it may be to define the normal condition of cells, at least we think it normal that cells should resist the displacement by other cells, particularly such foreign cells as those of bacteria. Normally the cells of the body are resistant to bacterial infection and the failure in this resistance is, in many cases, simply a failure to react,—a fatigue in the normal mechanism of defense. In the beginning, the defense is simply the healthy metabolism of the cell, the bacteria not coming in contact with the cell, or, if they do, the conditions normally do not favour the invaders. The fatigue of any cell makes it a more easy prey to the microbes. The mere massive onslaught of large doses of bacteria, as so often used in experiments may undoubtedly break down our defenses but such, in the natural history of infection only occurs under the rarest conditions. Bacterial invasion is very common but a recognized infection seldom follows. Infection

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depends upon the ability of the parasites to multiply in the host; this ability we call virulence, and it is developed and maintained in the host. We recognize disease only in those cases where the outcome has favoured the microbe, but we know little in most of our infections about these favouring conditions.

We have in the past undoubtedly over-emphasized the dominant position of the microorganism as the exclusive causative agent in the infectious diseases. The numerous factors which determine the invasion, the establishment of the microbe, the beginning development of virulence, the production thus of strains of bacteria capable of epidemic spread or of becoming a menace to the host,—these factors must be correlated and studied more critically.

The portals of entry in most of our infectious diseases are through the mucous membranes. The important defense against the first stoppage and primary colonization, when the bacteria have entered the oral cavity, is the simple mechanical removal by the flow of saliva and the mucous secretions in the rather definite courses so well demonstrated by Bloomfield.[2] Sufficient secretion for this purpose is therefore the first essential in this relatively simple defense. The conditions producing fatigue of this mechanism are more or less recognized but certainly not fully appreciated. The long continued breathing of dusty air tires the secreting cells and the mouth and throat become dry. A hot dry atmosphere may similarly cause fatigue by the excess activity in keeping the inhaled air moist, while a hot moist atmosphere causes almost as disastrous a result by the congestion and hyposecretion of a thicker, more tenacious mucus.

These cells are further brought under stress by reflexes from the skin in chilling, and an ischemia of the mucous membrane results. Among other factors, faulty diets of various kinds play a leading part. The striking replacement changes in the cells of the mucous membrane of certain parts of the respiratory tract from vitamin A deficient diets as shown by Wolbach[3], indicate that the whole functional activity of these cells may be lost. Hoelzel[4] has shown the importance in the production of colds, of edema or hydration of the organism, which develops under a restricted protein and a high carbohydrate diet. Chilling of the highly hydrated and sensitive skin throws an overload of fluid on the already overloaded respiratory tract and an excessive secretion follows. Cheney[5] has stressed a disturbance of the acid-base equilibrium with conditions favouring a mild acidosis, and advocated alkaline treatment. Many investigators have emphasized the beneficial tonic effects of regulated exercise and the harmful results of general fatigue, constipation and similar strains. The influence of all such factors must be carefully considered in arriving at a composite picture of the mechanism favouring infection. In its simplest form it may be said that a mucous membrane with a good reactive tone prevents bacterial localization and hence infection, while a tired mucous membrane failing to react, invites it. These infections may be the beginning of the most serious acute diseases such as pneumonia, or

the bacteria involved may lead to localized infections and the establishment of infected foci which serve the bacteria as outposts from which further invasion and infection may follow later, and such outposts often act as a long-drawn irritation to the body and may alter the whole type of cellular activity so that we develop the type of allergic reaction which Swift[6] and others have been studying in rheumatic conditions. Allergy in the cell is in many ways analogous to the familiar fatigue phenomenon in which an individual at a certain stage of tiredness is hyperactive, highly irritable and often does more harm than good to himself and his associates. Certainly in the rheumatic type of reaction the acute onset is frequently ushered in by a variety of events in which fatigue is a marked feature, and today more attention is being given to the factors bringing on this state in which a minimal stimulus brings about a maximal result. Fatigue of inhibitory mechanisms is a form of fatigue demanding more attention.

Under the circumstances of life, there is a far better hope that we may learn how to prevent the fatigue conditions of the respiratory tract than that we will ever be able to effectively interfere with the spread of oral bacteria from mouth to mouth.

The other common portal of entry for bacteria is the intestinal tract and it has other interesting and important bearings on the subject of fatigue and infection. Heavy exercise and fatigue definitely interfere with gastric secretion largely due to the disturbance of circulation. Another recognized factor is the external temperature and for much the same reason. The effect of this lessened secretion results in an increase and change in the bacterial flora of the upper part of the small bowel due primarily to decrease in the disinfecting action of the hydrochloric acid. This is of particular importance in young infants during hot weather but is certainly not confined to them. We know comparatively little about the conditions favouring the primary infection in even such a well studied disease as typhoid fever, but there is evidence to suggest that here again the healthy mucous membrane is remarkably resistant. Intestinal irritation with diarrhea or constipation plays a part in the invasion, and much experimental evidence indicates the importance of diet and the external temperature. Sir Leonard Rogers[7] has correlated the rise in the absolute humidity (which occurs in warm, muggy weather) with the rise in the incidence of cholera in India and might not this be partially explained by the reflex fatigue effect on the intestinal mucosa from the congestion in the skin. The seasonal variations in the occurrence of intestinal diseases have not been adequately explained.

Constipation is of many kinds but in its consideration we must not neglect the importance of fatigue. The general effect of constipation is at first a stimulation as manifested by flushed skin and a feeling of general well-being. This is followed by a stage of capillary fatigue with cutaneous pallor, headache and general depression,—all evidence of faulty circulation. These are the symptoms of autointoxication and a bowel movement relieves them so promptly that it suggests such a

reflex mechanism as the cause. Such disturbances in circulation are felt in all parts of the body and have an important effect on bacterial infection. It is common practice in the treatment of many kinds of infection to take precautions against constipation and the remarkably rapid cures after the use of laxatives are otherwise difficult to explain. Vitamin B deficient diet brings about intestinal stasis, and a deficiency in vitamin A a tendency to diarrhea, and it is the fundamental cellular changes which result from these deficiencies which must be included in the many factors bearing on the fatigue of the defense mechanism against bacterial infection of not only the mucous membrane but all the other tissues of the body. Flinn,[8] in a study to determine the action of acid sodium phosphate in delaying fatigue concluded that the good results were due to the beneficent stimulation of the intestinal tract.

Boycott and Price-Jones[9] have demonstrated a marked increase in the susceptibility of fatigued rats to fatal infection after feeding the Gaertner bacillus, although no such effect was noted after subcutaneous or intraperitoneal injections.

Invasion from the intestinal tract occurs much more frequently than is generally realized but under normal conditions the bacteria are stopped and destroyed in the liver, glands and other organs.

There must be more than mere passage of bacteria, into or through these outer defenses, before an infection will follow. It takes time for the invading organisms to establish themselves in some favourable location where they are able to multiply, adapt themselves to the new environment and overcome the immediate defense if they are to bring about an infection. The numerous failures on the part of the invaders pass unnoticed and we fail to appreciate how effective the normal defense really is.

There are so many types of infection that it would be impossible to consider them all at this time. The idea I would here emphasize is that under the stress of infection, fatigue much more readily ensues. The rationale of all treatment is to prevent this overwork so that the cells may return to their normal metabolism and regain their resistant tone. The difficulty is to determine what may be the factors inducing fatigue. Sometimes too much, sometimes too little of a special constituent of the diet, general muscular overwork and, perhaps more frequently, underwork, excess in cutaneous reflexes of various kinds, worry and a thousand and one things lead to the lowering of reserve energy and thereby prevent the recovery.

There are, however, certain localizations in which the difficulty in obtaining mechanical rest plays the dominant rôle in keeping up chronic and even acute infections. The infected foci about teeth and tonsils, the infected ulcers in the stomach and duodenum, and in the colon are examples of those difficult to keep at rest.

In the tonsils, primarily infected under the circumstances of invasion already discussed, incident follows incident until there is a chronic infection deep in the thin-walled crypts of the tonsil where there develop ulcers surrounded by numerous blood capillaries.

In the act of swallowing, the tonsils are definitely massaged which undoubtedly forces bacteria into the circulation, the numbers increasing under acute exacerbations because of actual increase in the bacterial population and the increased blood flow associated with the inflammation. Patients with tonsils of this kind become conscious of the infection under a variety of fatigue conditions, the margin of safety being much reduced. The tonsillar infection also plays a part in inducing the fatigue and it is the vicious circle thus established that makes so difficult the interpretation of the primary causes of the fatigue syndrome. Although many preventive measures may help to protect against the original fatigue conditions which permitted the primary infection, once this becomes established, it is the most important complication and the tonsils should be removed, principally because of the potentiality of the bacteria for infinite multiplication at the expense of the host. It is too much to expect, however, that the elimination of such foci will in all cases simultaneously remove the original causes of the fatigue state, but very often it does give invaluable aid in re-establishing a better cellular tone and resistance.

We have similar conditions to consider about the teeth. Corresponding to the thin epithelial lining of the tonsillar crypts we have in the gingival crevice the weakest link in the chain of epithelial covering in the mouth. There is further a very rich capillary blood supply which in cases of pyorrhea is increased. Pyorrhea develops in the great majority of cases because of unusual strain on the gingival tissue. The commonest cause of this strain is malocculsion with its continuous excess pressure on one side and drag on the other. There is, of course, normally a good deal of movement of the teeth which is a healthy stimulus to the surrounding tissues but when this becomes excessive, fatigue ensues and all manner of mouth bacteria and even amebae move into this area of lowered resistance. The effective cure of pyorrhea is to adjust these stresses; this gives relative rest to the tissues and there usually follows a remarkably rapid return of the normal tone and with this an automatic elimination of the infection.

When periapical infection has resulted from the many familiar causes, it is the continual movement of the teeth which prevents cure. This movement is not only in mastication but practically every time we swallow. The problem of discovering this type of infection is beset with difficulties. Dental films, although most valuable, are of limited use and may lead us astray. There is, however, a clinical observation which has not been sufficiently stressed but which may be helpful in this maze of confusion. It is the frequent evidence of tenderness about areas of active infection which is only noticed when the individual is tired out physically or mentally. Taking advantage of such general fatigue in discovering the sites of infection where, because of the infection, the normal reserves are at a minimum and unusual reactions occur, is, I believe, a method not widely enough used or appreciated. Certainly every clinician knows and uses such methods in a general way. Our weak spots become evi-

dent under stress but it is perhaps not sufficiently recognized that the activities of infected foci rise and fall in inverse ratio with the rise and fall of the bodily reserves.

The factors favouring the production of gastro-duodenal ulcers are not unlike in principle those we have mentioned for other areas. The disturbing effects of mental strain and worry, the use of locally irritating and hyperstimulating foods and the numerous reflexes affecting the circulation and hence the activity of the secretions and the metabolism of the cells, all may lead, alone or in combination, to the point of cellular fatigue where infection again complicates the process. The frequently satisfactory results of simple means of giving rest certainly speaks against the primary dominant importance of bacteria in the etiology, but should not blind us to their extremely dangerous rôle in complicating the condition and where their source is in other infected foci these should certainly be attended to.

Chronic ulcerative colitis is often the aftermath of amebic or bacterial dysentery. In the idiopathic types the etiological factors are far from being clear. We are still under the spell of the early days of bacteriology. We want to discover a specific etiological cause. In my opinion we would better focus our attention on obtaining more precise ideas of the physiology of the colon; the effects of diet not only on the intestinal contents but on the nutrition and healthy metabolism of the bowel wall; the whole question of nervous impulses to and from the colon; the reasons for the extremely high incidence of constipation more or less chronic or alternating with conditions of diarrhea. I have endeavoured to keep before me these principles of fatigue and infection in an attempt to correlate what we know about the health and diseases of the colon. Ulcerative colitis is to me a stage in a long process in which the previous stages have often gone undiagnosed, which is also true for most of the other conditions of infected foci I have discussed. The bacterial infection is very important locally but these ulcers may further serve as portals of entry for bacteria to the rest of the body. The complicating bacteria are, however, in my opinion, those of the individual patient.

In the infections of other organs and the localizations of bacteria which have invaded the blood stream, we should consider as a most important factor the probability of overwork and fatigue not only of the whole body as in muscular exercise, but in the hyperactivity of any organ or tissue lowering its reactive resistance to the establishment of infection. A number of experiments such as those by Spaeth[10] tested the resistance of animals after forced running by means of intraperitoneal injections and found it raised. The greatest fatigue, however, in such cases is apparently in the mucous membranes and not in the serous cavities.

Exercise of all the functions of the body is the surest way to prevent infection by building up a reserve of reactive energy to meet emergencies. The trained athlete from long experience and empirical practice has learned that after active exercise it is dangerous to slow the circulation too rapidly

so he wraps himself in warm blankets, is massaged and has a "rub-down." The ordinary individual feels superior to such treatment and in such cases unaccustomed exercise often results in more harm than good. During exercise, bacteria may readily enter the blood stream through the dilated capillaries about infected foci when such exist but the chance of these bacteria being stopped in those organs responding to the stimuli is probably at a minimum. After exercise the sudden closing of capillaries and the slowing of the circulation not only favours localization of bacteria but because of the failure to remove the excess metabolic products, offers in the fatigued tissues, areas of lowered resistance to infection. All such conditions of fatigue do little more than temporary harm unless complicated by infection and the very real menace from infected foci depends on this fact.

The far more common type of fatigue is from long continued stimuli of many kinds which result, not in healthy reaction but rather in the fatigued state of sluggish and delayed reaction. The fatigue associated with infection is far more frequently the result of under than of over-exertion. The outstanding significance of fatigue in diseases like tuberculosis need only be mentioned but it should be realized that our success in the treatment and prevention of this disease has been almost exclusively due to the recognition of the factor of fatigue.[11]

The therapeutic use of rest is the basis of practically all our methods of treating established infection. Every effort is made to reduce to a minimum any accessory calls on the infected tissue so that its entire metabolism may be devoted to its recovery. How effectively we obtain this rest largely depends on how thoroughly we understand the metabolism of the cells and how well we are able to bring about, in addition to the general rest, the physical local rest of the part.

As a student at McGill many years ago, I was much impressed with that surgical classic, Hilton's "Rest and Pain." The principle he outlined still holds good,—the obtaining of physical and physiological rest by every means in our power where Pain is the monitor and Rest the cure. Today we may somewhat extend the principle and say with Fatigue the warning, Pain the monitor, Infection the punishment and Rest the cure. Fatigue and Infection—our efforts should be directed to know more and more about the earliest onset of each for they bear a close relationship to each other and the subject is in my opinion at the very foundations of preventive and curative medicine.

After all, a paragraph in one of our daily papers under the heading "Isn't it the Truth?" gives pretty nearly the gist of what I have been saying. It says, "The reason there were so few fatalities in the recent epidemic of influenza was because he-men were not ashamed to stay in bed."

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Tobacco Smoking and Gastric Symptoms*

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THE increasing incidence of tobacco smoking and the increasing frequency of functional gastric disorders prompted the following study, in order to correlate the occurrence of gastric symptoms and tobacco smoking, as well as to determine, if possible, the effect of tobacco smoking in individuals with organic gastric disease. Observations have been recorded during the past five years on all patients who presented themselves with gastric symptoms and who gave an associated history of tobacco smoking. For purposes of study, 400 individuals were chosen and divided into two groups. In Group A were placed 300 patients who had functional gastric disturbances and who gave a history of tobacco smoking. In Group B were placed 100 patients with organic gastric disease who gave an associated history of tobacco smoking. The ages of the patients in both groups ranged from 25 to 65 years, and there was a history of tobacco smoking for at least 5 years. Of the entire group under observation 5 per cent were women. They all presented gastric disturbances which were functional in nature.

The chief poison in tobacco is nicotin. Other products which are formed in the process of combustion are chiefly pyridin, ammonia, and carbon monoxid. These products have a secondary and very slight effect on the system. That nicotin is the principal agent of tobacco that causes gastrointestinal disturbances has been pointed out by Cramer, Lickint, Noah, Rolleston, and others. Nicotin is one of those alkaloids that has a peculiar affinity for the autonomic nervous system, first stimulating and then depressing the sympathetic and parasympathetic ganglia. The explanation for the fact that nicotin exerts a greater action on the sympathetic is, in the opinion of Cannon, Aub, and Binger, due to an increased output of adrenalin. After nicotin injections in animals they examined the blood of the vena cava and were able to prove that there was an increase in adrenalin output.

Skaller, in animal experimentation, came to the conclusion that nicotin acted through the blood-stream on the ganglion cells in the gastric wall, and not in the sense of increased secretion of the secretory glands, for after injections of atropin the nicotin lost its action. This author also showed that it was not the nicotin saliva that caused the gastric flow, because after subcutaneous injections of nicotin sub-

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stances there followed an increase of gastric juice.

When we come to the question of symptoms in human beings which may be associated with the use of tobacco, we cannot altogether apply experimental observations on animals after use of pure nicotin to clinical results on humans. It should be remembered that the action of nicotin is continuous during the entire day in human beings, and that the symptomatology is not only the result of a local action on the tongue, the mouth, and the gastric mucosa, but mainly the result of stimulation of the vegetative nervous system. We find in the stomach ganglion cells whose chief function it is to promote all automatic movements after complete severance of all extrinsic nerves. We know also that both motor and secretory fibers are contained in both components of the vegetative nervous system.

The question as to the exact manner in which tobacco smoking may produce gastric symptoms cannot be definitely answered, for even after animal experimentation there are conflicting opinions. Results that are obtained in animals surely cannot be applied to the human, who readily establishes a tolerance to nicotin and smokes a nicotin containing product and absorbs, or swallows, varying amounts.

The individual sensitivity to nicotin and the art and manner of smoking have a great deal to do with gastric symptomatology. Bogner has shown that the inhaler absorbs eight times more nicotin than the mouth smoker.

Dixon states that nicotin is one of the most fatal and lethal poisons known, and the amount present in one cigar, if injected intravenously, would represent two fatal doses to man. This author also states that the effects induced by smoking are entirely due to this principle: during smoking a part of the nicotin is burned off and a part is inhaled with the smoke as free nicotin. The drier the tobacco the greater is the destruction of nicotin. Moist tobacco evolves more nicotin and produces more serious effects than dry tobacco. It has been stated that the moistness of tobaco is chiefly responsible for many of the evils of smoking. The moist content of the tobacco must, therefore, be considered as more harmful to the smoker than the actual amount of nicotin. During the slow combustion of a cigar in ordinary smoking there is an area immediately behind the point of combustion in which the active principles of the smoke condense. During aspiration the solid gases are drawn through the moist and cooler area, carrying with them the volatile principles, of which nicotin is the most important. The cooler the smoke and the more complete the combustion, the less likely is the smoke to contain volatile toxic bodies. A cigarette or a slender cigar, as it is cooler than a thick cigar, will yield fewer of the toxic products. Many smokers realize that a fat cigar is more powerful in its effects than a long slender cigar of similar tobacco. This also explains the unpleasant effects of relighting a half finished cigar. In smoking, the degree of moisture, the tightness of the packing, the thickness of the cigar or cigarette are the most important factors in determining the amount of nicotin which will be present in the smoke. Lehman has

shown that from 1 gram of cigar there is retained, or absorbed, from 0.3 to 0.8 gram of nicotin, and from 1 gram of cigarette from 0.4 to 0.5 gram will be retained. It must not, however, be assumed that all the nicotin in the smoke is necessarily absorbed into the system.

In the analysis of the 300 patients comprising Group A, or those with functional gastric symptoms and tobacco smoking we made the following subdivisions:

1. Heartburn 180
2. Duodenal ulcer symptom-complex 51
3. Gastrocardial symptom-complex 16
4. Gastrospasm (including cardiospasm and pylorospasm) .. 30
5. Gastritis? (anorexia, malnutrition, etc.) 23

In the study of these 300 patients thorough examination was made in order to exclude organic disease in either the stomach or other organs that might account for the symptomatology. After careful history taking and physical examination, complete laboratory investigation, including chemical, serological, and roentgen studies, were done so that we were confident the symptoms present were functional in nature.

1. Those patients who presented themselves with heartburn as their principal symptom formed the majority in this entire group. Heartburn is not a disease, but a symptom due to regurgitation of gastric contents into the esophagus. As pointed out by Hurst, the mucosa of the esophagus is distinctly sensitive to chemical stimuli, and it is the presence of gastric contents in the esophagus that is responsible for the symptom designated as heartburn. In many of these individuals heartburn was associated with a burning sensation, either in the epigastrium or in the throat. It was not dependent upon gastric hyperacidity, as has been frequently shown. In this series, of 180 patients, 97 had normal gastric acidity, 44 had hyperacidity, 37 had subacidity, while 2 had anacidity.

The frequency of heartburn in many patients with gastric symptoms, due either to local or to remote causes, has never been satisfactorily explained. Perhaps the increased salivation that accompanies smoking is frequently swallowed and the saliva in its passage through the cardio-esophageal junction at frequent intervals during the day may allow of regurgitation of gastric contents into the esophagus, thus producing heartburn. The intensity and duration of this symptom varied greatly, but was especially evident when the individual smoked between meals or on a "fasting" stomach. Some of these patients had to take bicarbonate of soda for relief of their symptoms. The amount of smoking was no criterion for the occurrence of heartburn. Approximately one-fourth of the entire number had this distressing symptom, although they smoked comparatively little. Cessation of smoking would bring about relief within 24 to 48 hours, but heartburn would recur if the patient resumed smoking. In some of those who smoked quite heavily the removal of tobacco would in the beginning be associated with loss of appetite and with gastric disturbances. It was difficult to decide whether these symptoms were

dependent upon organic changes or upon suggestion.

2. There were 51 patients, or approximately one-sixth of the entire group, who gave, upon history taking, the symptom-complex commonly met with in duodenal ulcer. Pain one to three hours after meals with epigastric distress, relieved by alkalies, was the usual story. Several of these patients had mild attacks of pain during the night, which was relieved by the taking of bicarbonate of soda. Repeated fluoroscopy and x-ray study failed to reveal any evidence of duodenal ulcer.

That symptoms of duodenal ulcer can be produced by the excessive use of tobacco was called attention to by Wagner. In heavy cigarette smokers Adler also obtained a history that closely resembles that of peptic ulcer. In this group 40 of the 51 patients were between the ages of 40 and 52 who gave a history of the use of tobacco for a period of more than 15 years. The question of tobacco smoking as a factor in the production of peptic ulcer and gastric neurosis was investigated by Barnett, who states: "There is no proof that smoking is of any importance in the etiology of peptic ulcer or gastric neurosis, and secondly, there is no proof that smoking has any effect upon the age of incidence of gastric or duodenal ulcer." These individuals who present the symptom-complex of duodenal ulcer at times tax the ingenuity of the examiner, and the question of a probable mucosal ulcer in the first portion of the duodenum, despite the negative x-ray, might be entertained were it not for the fact that with the cessation of smoking the symptoms would gradually but definitely disappear. If after the disappearance of symptoms these patients were allowed to smoke, there would be a return of their subjective symptoms within one week. Fractional gastric analysis showed a hypersecretion in practically the entire group. Hyperacidity was present in 20 per cent of these patients, the remainder having normal acid figures. In none of these individuals was there a subacidity.

3. There were 16 patients who presented the symptom-complex described by Roemheld as the "gastro-cardial symptom-complex." They were all between the ages of 50 and 65, and gave very little variation in their history. Occasional feeling of anxiety, tachycardia, oppression in the region of the lower chest, or in the upper epigastrium, breathlessness, slight distress after eating—coming on shortly after food—and the ages of the patients gave one the impression that the underlying lesion was probably arterial or cardiac in origin, rather than gastric. Some of these upper abdominal symptoms may have been due, as Rolleston states, to attacks of angina abdominis, precipitated by spasm, induced by smoking, similar to angina pectoris arising from coronary artery spasm. Because of the age of the patients and the predominating cardiac symptoms, studies of gastric chemistry were not made in this group. Moderation in the use of tobacco brought about improvement in their symptoms. Three of the patients who ceased smoking entirely had complete relief of their distress.

4. Gastrospasm, including cardiospasm and pylorospasm, occurred in 30 patients. Of this number 6 had

a distinct cardiospasm of varying intensity only upon tobacco smoking. Two of these patients were physicians who had become so sensitive to tobacco smoking that the use of one or two cigarettes would produce a feeling of distress behind the sternum and upper epigastrium. All these individuals were of the nervous type, very active in their work, rushed through their meals, and were heavy smokers. Fluoroscopic examination of this group with cardiospasm showed a slight delay in the passage of the barium meal through the cardioesophageal orifice with increased retroperistalsis. Cessation of smoking brought about relief of symptoms, but a complete return to normal did not follow until about two months after smoking had been entirely discontinued.

Pylorospasm occurred in 22 of this group. There were others in the entire group (Group A) who presented occasional clinical symptoms and had x-ray evidence of mild gastrospasm who were not included in this study. These patients under discussion had definite signs and symptoms of pylorospasm which had persisted to a varying degree for months. Their symptoms would usually come on from two to four hours after meals, and the distress would always be aggravated upon smoking. According to Carlson and Lewis, the hunger contractions of the empty stomach on smoking depend upon the strength of the tobacco. It is interesting to note that in three of these patients with pylorospasm tobacco smoking, when the individual was "relaxed," would bring about relief of symptoms. The ages of the patients in this group varied from 26 to 40 years. One-third showed a distinct gastric hyperacidity, and two-thirds showed normal acid values. There were no patients with subacidity or achylia.

Upon fluoroscopy there was increased tone and peristalsis in all these patients. The spasm of the pylorus varied in intensity and duration, but there was no paradoxical residue, and the emptying time was normal.

One of our patients, H. R., a young man of 28, had symptoms of pylorospasm of varying degree, and because of an attack of hematemesis was admitted to the hospital. Prior to his admission, repeated fluoroscopy and x-ray study failed to show any evidence of ulcer, but there was always a marked spasm of the pylorus. Because of his subjective symptoms, which terminated in an attack of hematemesis, operation was performed. A most careful examination of the stomach and duodenum failed to reveal any evidence of ulcer. This young man was in the habit of smoking from 30 to 40 cigarettes a day for five years prior to his operation. After his recovery, cessation of smoking brought about a gradual improvement in symptoms and he has remained perfectly well since.

5. In the final classification of those who presented functional gastric disorders and gave a history of tobacco smoking were grouped 23 patients who complained of anorexia, abdominal distress of varying nature, gastric disturbances, and who were underweight. In several instances, because of the emaciation, carcinoma of the stomach was suspected. The ages of these individuals ranged from 45 to 63. Frac-

tional gastric study showed normal acidity in 3, subacidity in 14, and anacidity in 6. Because of their symptoms, general appearance, and chemical findings, the diagnosis of a probable gastritis was made.

Fluoroscopic examination showed a decrease in tone and peristaltic activity, and an increased emptying time because of a somewhat patent pylorus. In none of these patients was there a history of diarrhea as occurs in some individuals with a gastric anacidity. In a special study of 6 patients who had a subacidity and in whom tobacco had been withdrawn for a period of three months there was no increase in appetite, and very little increase in weight.

The pathologic-anatomic findings in the stomachs of tobacco users are not very well known. Local changes, such as ecchymosis, inflammation, and punctuate areas of erosion in the gastric mucosa of animals that had died of nicotin poisoning, have been reported by Taylor. A chronic catarrhal process of the mucosa was reported by Grossman and Giano as occurring in dogs that had been fed for a period of several months on a watery solution containing nicotin.

Group B was comprised of 100 patients with organic gastric disease who gave an associated history of tobacco smoking. In this group were:

1. Duodenal ulcer 63
2. Gastric ulcer 12
3. Carcinoma of the stomach ... 6
4. History of ruptured duodenal ulcer successfully operated on by closure of the perforation 2
5. History of posterior gastroenterostomy for duodenal ulcer 17

All these patients had been under care for at least nine months, and the relationship between tobacco smoking, clinical symptoms, and gastric secretory findings had been noted. The diagnosis in each case had been established by the x-ray examination, or by surgery.

1. In the duodenal ulcer group tobacco smoking was found to cause an increase in secretion in 50 of the 63 patients. If the patient smoked before breakfast, there was found almost constantly an increase of secretion of 10 to 20 c.c. in the fasting stomach content. Smoking caused an increase in acidity in about one-fourth of the entire group. Two patients showed distinctly lower acid figures after tobacco smoking. In the remainder the gastric acid curve was unchanged.

In 35 of these patients active clinical symptoms were present. The amount of tobacco used varied greatly. It was difficult to decide, because of the individual sensitivity, in what manner to curtail the consumption, and it was, therefore, deemed advisable to exclude the use of tobacco entirely in order to see what effect complete abstinence would have. The patients' co-operation was invited and the purpose of the test carefully explained.

We who are tobacco users know how difficult such restrictions are. All these 35 patients promised faithfully to adhere to the test for one month. All had been under ambulatory treatment prior to the test and were told to continue as heretofore, except that smoking was to be entirely discontinued. With the cessation of smoking there followed improvement in symptoms in 6 patients within one week. At the

end of a month 11, or approximately one-third of the entire number, reported distinct improvement. In the remainder subjective symptoms of a varying nature persisted. In 3 of the 11 patients who showed a distinct improvement there was loss of night pain, which had been one of their troublesome symptoms. When these individuals resumed tobacco smoking, clinical symptoms reappeared in about three to six weeks.

2. In the 12 patients with gastric ulcer tobacco smoking caused a hyperacidity in 5. Three patients showed a subacidity after tobacco smoking. Four were unaffected. Cessation of smoking for a period of one month brought about clinical improvement in only 2 of this group. Both these patients showed a hyperacidity after tobacco smoking.

3. Tobacco smoking had no relation whatsoever either to the subjective symptoms or to the clinical findings in the 6 patients with carcinoma of the stomach. The withdrawal of tobacco in no manner altered their subjective symptoms.

4. The 2 patients who were under observation and who had been operated on for ruptured duodenal ulcer showed no change in their gastric secretory findings after tobacco smoking. One of these patients had frequent heartburn which was relieved after cessation of smoking, but the pain which occurred between meals was entirely unaffected.

5. Of the 17 patients who had a gastro-enterostomy performed for duodenal ulcer it was difficult to determine any acid values after tobacco smoking because of regurgitation of intestinal contents. The withdrawal of tobacco in 7 of these patients who had active clinical symptoms brought about an improvement in 3.

Excluding the 6 patients with carcinoma of the stomach, there were 94 adults with organic gastric disease, Approximately half of them presented themselves because of clinical symptoms and gave an associated history of tobacco smoking for a period of from five to thirty years. The active symptoms either disappeared or were ameliorated in about 80 per cent of this entire group, under proper medical management. In the remainder, despite medical treatment, there was persistence of symptoms, and it was not until tobacco was entirely withdrawn that active symptoms began to disappear and improvement followed. Some of these patients because of hunger pain would smoke, and although they had temporary improvement, occurrence of pain of greater severity would follow in a short time. With the relief of symptoms after tobacco had been withdrawn and comfort restored, the smoking of a few cigarettes was sufficient in some of these patients to bring about a return of symptoms. Apparently these individuals had become so sensitized to tobacco that they could not tolerate even the smallest quantity. In some patients smoking would cause a loss of appetite, and perhaps the pain could be ascribed to the fact that food was taken at very irregular intervals.

In order to obtain more definite data on the gastric motor and gastric secretory response to tobacco smoking, 50 patients of Group A and 50 patients

of Group B were studied more intensely.

From Group A were chosen 10 patients from each of the five subgroups. These patients were all fluoroscoped on several occasion. The first fluoroscopic examination was made with the patient fasting so that data might be obtained as to the normal tone, peristalsis, size, shape, and position of the stomach. During the second examination the individual was allowed to smoke shortly after the barium meal was given. The blue light was on during this examination, so that the individual might see the smoke. Many of the patients did not enjoy smoking in the dark, and in order to have as normal a condition as possible, some light was allowed in the room. The third fluoroscopic examination was made after the individual had smoked on a "fasting" stomach and prior to the administration of the barium meal.

Fluoroscopic examination of the 10 patients selected from the group designated as having a probable gastritis showed a very little change either in the tonus or in peristaltic activity, whether the individual smoked before or after the barium meal was given. In the 10 patients chosen from the group designated as "gastro-cardial," smoking prior to the administration of the barium meal caused an increase in gastric tonus and in peristalsis in 2 of these patients. In 3 there was a decrease in tonus and in peristalsis if smoking were allowed after the barium meal was given. In the remaining 5 no change was observed at any time.

Peristaltic activity and gastric tonus was definitely increased in 22 of the remaining 30 patients. These individuals had the most pronounced clinical symptoms in the groups designated as heartburn, "duodenal ulcer symptom-complex," and gastrospasm. Smoking prior to the administration of the barium meal produced a more marked gastric response than if smoking were allowed after the barium meal. On both occasions, however, there was an increase of peristalsis above the normal. In none of these patients was there any delay in the gastric emptying time. The increase in peristaltic activity would last from ten to fifteen minutes and then the contractions would decrease and become normal, and in some patients distinctly weaker than normal.

Danieleopolu and his co-workers report that in their studies x-ray examination showed a tendency to paralysis of the contracting power of the stomach starting ten to fifteen minutes after the first inhalation of smoke and persisting over an hour. This paralysis was often preceded by a phase of hypercontractibility and occurred with large amounts of tobacco smoke. It is assumed that small doses may stimulate the contractibility.

In studying the gastric secretory changes in these 50 individuals fractional analysis was done in the usual manner so that a curve for each was obtained. In those patients who showed a hyperacidity or a sub- or anacidity, fractional study was repeated to corroborate the primary findings.

In the 10 patients selected from the group stated as having a probable gastritis, smoking prior to the test meal study showed practically no change in

the acid findings, other than a slight increase in the amount of "fasting" gastric secretion. If the individual smoked one hour after the test meal had been given there was a slight increase in gastric acidity, but no distinct rise, and practically no change in those patients who had a subacidity.

In the 10 patients selected from the group designated as "gastro-cardial," tobacco smoking prior to the giving of the test meal showed an increase in secretion, but no increase in acidity. When smoking was allowed after the test meal had been given in 6 of the 10 patients there was a decrease in gastric acidity which started within fifteen minutes after smoking was allowed and lasted during the entire study.

In the remaining 30 patients of this group (functional), after their normal gastric curves were obtained they were permitted to smoke prior to the giving of the test meal and one hour after the meal had been given. The duodenal bucket was in the stomach during the entire examination. Smoking prior to the test meal caused an increase in gastric secretion in one-half of this group. In about 20 per cent of this number there was in increase in acidity during the first hour, but in the second the gastric curve was similar to the normal one. If smoking was allowed one hour after the test meal was given, there was a distinct rise in figures above normal in about one-third of the entire number. Tobacco smoking at the end of the second hour period would again produce an increase in secretion, although the acid figures did not rise. These tests were repeated on several occasions and the chemical findings were practically the same at all times.

Many brands of cigarettes were used in this group, including some of the alleged nicotin-free products, and there was practically no change in the findings.

It is of interest at this time to call attention to the findings of Bailey and his coworkers in their studies on "denicotinized" tobacco. According to their results, "denicotinized" products vary considerably in nicotin content. As a group, these products were found to contain less nicotin than tobacco, but practically all contained varying amounts, some even containing as much nicotin as is found in ordinary tobaccos. The results of their investigations are important for the reason that some individuals who are advised to discontinue tobacco smoking substitute these "denicotinized" products and may equal or exceed their usual consumption of nicotin. Frank also found approximately as much nicotin in alleged nicotin-free products as in normal tobacco.

The 50 patients chosen from Group B all had definite evidence of duodenal ulcer. The patients were males between the ages of 25 and 45 who had had symptoms for two or more years and had been smoking for at least five years.

Fluoroscopic study was first made to determine the tonus, peristalsis, and motor activity so that a conception of the normal activity of each stomach might be obtained. Many of these examinations were repeated to confirm the original findings. About one-half of the entire number were in the

quiescent stage, but all the patients were under medical supervision.

If fluoroscopic study was made after the individual had smoked on an empty stomach, there was an increase in peristalsis and in tonus in 10 per cent. of the entire group. Three patients had a paradoxical residue (Haudek) after four hours, which did not occur when the control study was made. Smoking one-half hour after the barium meal did not alter the peristalsis, although there appeared to be slight increase in tonus.

In order to study the secretory changes which occur after tobacco smoking, at least two fractional analyses were done on each patient prior to the tobacco test. Seventy per cent. of the group showed the usual acid curve for duodenal ulcer as described by Rehfus. There was a distinct increase of gastric secretion with high acid figures on the fasting stomach in 60 per cent of the group. If the patient was permitted to smoke prior to the giving of the test meal, there was an increase in the amount of fasting content. Fractional curves of test meal studies, after smoking was permitted on an empty stomach, showed a higher curve during the first hour with findings similar to the original studies during the second hour. If smoking was allowed at the end of one hour after the administration of the test meal, there was slight increase in acidity, and in a few instances there was a decrease in the acid figures. If the individual smoked at the end of the two-hour period, there occurred in about half the number a definite increase in the amount of gastric secretion and in the acid values. This lasted for about one-half hour. Three of the patients on repeated study showed a decrease in acid values after tobacco smoking, whether allowed to smoke prior to or one hour after the test meal was given.

Most of the patients studied in both groups were cigarette smokers. Approximately one-fifth of the number smoked cigars only, some smoked cigars and cigarettes, and very few smoked a pipe. The technique of smoking and the individual sensitiveness to nicotin varies greatly and undoubtedly accounts for many of the gastric disturbances and for the fact that not all tobacco smokers are affected alike. Gastric symptoms and findings will depend upon whether or not one is a dry smoker, on the amount of tobacco which reaches the mouth, on the question as to whether or not one is in the habit of chewing the end of a cigar, and as to whether or not particles of the tobacco are swallowed. A great deal of nicotin usually collects in the stump of a cigar, and if the lower one-third of the cigar is not smoked, less nicotin will be burned and less will be absorbed.

On history taking it is, therefore, important to note not only how much, but also the art and manner of smoking. Although tolerance is easily acquired and habitual users may tolerate as much as 40 milligrams a day, the measurements of the amount of nicotin retained in the smokers, either swallowed or absorbed, vary greatly.

Gastric response to tobacco smoking may be due either to the action of nicotin on the ganglion cells in the gastric wall or to the action of nicotin (when swallowed with the saliva) directly on the gastric epithelial cells or

may be secondary to gastric blood-vessel changes due to the action of nicotin.

Conclusions:—

1. Tobacco smoking should be considered an etiological factor in gastric functional disturbances.

2. Individual sensitivity, rather than the amount of tobacco consumed, appears to be the determining factor as regards symptomatology.

3. Gastric secretory and gastric motor response in individuals with functional gastric disturbances due to tobacco smoking vary, despite the similarity in clinical symptoms.

4. Approximately one-fourth of individuals with gastric functional disturbances attributable to tobacco smoking show a hyperacidity, and about one-fifth a subacidity.

5. In peptic ulcer tobacco smoking usually causes an increase of gastric secretion during the fasting stage, and a hyperacidity in about one-third the number.

6. Clinical improvement in some of these patients with ulcer occurs only after cessation of smoking. The withdrawal of tobacco in these patients is most advisable.

7. The therapeutic test, and not the chemical and roentgen findings, is the criterion as to whether or not the individual should smoke.

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Editorial

POST-VACCINATION ENCEPHALITIS

During the month of July of this year, much attention was given in the British press to comments upon deaths from encephalitis following vaccination, and to issues of great public importance thereby raised. Two of the cases arousing particular interest occurred in a girl aged fourteen and in a boy of twelve years, the first dying one month after vaccination and the second three weeks after. Both had symptoms of encephalitis developing on the 10—13th day after vaccination, and in both the autopsy examination of the brain and cord showed lesions characteristic of "post-vaccinal encephalomyelitis." There was nothing in the evidence to indicate anything abnormal about the method or the course of the vaccination, the coroner's verdict stating that there was no suggestion in the evidence that the vaccination had been otherwise than properly and skilfully carried out. The coroner's verdict in each case was "Death by misadventure". Commenting further, the coroner stated that this was the third case of the kind he had investigated within the last month; and that it is "disquieting to think that these cases are occurring more frequently than formerly. It is also disquieting to think that however careful one may be in the preparation of the lymph and in the methods of administration, this disease may occur from time to time. Very little is known of this condition."

Commenting upon the case under question the pathologist, Professor H. M. Turnbull, stated that the occurrence of postvaccinal encephalomyelitis was now recognized generally to be connected in some way with vaccination. This connection was first shown in the London Hospital in 1922. It was recognized in Holland in 1925, and since then has been found in nearly every country. It was not considered by him to be a new disease, although apparently becoming more common. It had not been found that the disease was due to any fault in the preparation of the lymph or to any contamination. The exact cause had not yet been discovered. Some considered that this disease was due to the vaccinal lymph itself acting on persons who were abnormally sensitive to it. Most investigators believed that the vaccinal lymph lighted up infection which was lying dormant in the patient. The latter view had support in the observation that a very similar inflammation might complicate measles. All authorities are agreed that the disease has nothing to do with encephalitis lethargica or infantile paralysis. The illness is usually well defined on the 10th to the 13th day after vaccination. It may begin earlier or a little later. It has never begun months or years after vaccination. The disease may occur in infants under one year of age. When

all vaccinations are taken into consideration this complication of vaccination is extremely rare. According to the report of the Committee on Vaccination, Ministry of Health, 1928, there were 62 cases between October, 1922, and December, 1923, inclusive; approximately one case in 16,903 vaccinations. Very few of the reported cases were confirmed by microscopic examination. The great majority of cases had not been vaccinated before. In one of Turnbull's cases, there was a history of a previous vaccination but no scars of a successful take. "About half of those affected die, but the remainder, with few exceptions, recover completely."

In the "League of Nations" report on the subject, it is stated that "in our present state of knowledge, we must conclude that postvaccinal encephalitis is a different disease from encephalitis lethargica. The conditions under which postvaccinal encephalitis has manifested itself in the Netherlands and in England and Wales tend to show that children between 3 and 13 years of age are particularly susceptible, while infancy (disproved by Turnbull) and adult ages are almost wholly exempt. All observations point to the conclusion that the appearance of encephalitis is not connected either with particular strains of lymph, or with particular accidents of lymph preparation.

Passing to the etiologicopathological side of the problem, it would appear that in our present state of knowledge the virus of vaccination of itself cannot be considered responsible for the supervention of encephalitis. Rather it is to be supposed that some unknown factor exists—perhaps bacterial or a filtrable virus, or a latent virus which by means of a reciprocal reaction determines the occurrence of the accidents in question.

The Report of the Committee on Vaccination, of the Ministry of Health, headed by Sir Humphrey Rolleston, issued in 1928, is an elaborate work of 322 pages with many charts and tables, in which the whole subject of diseases of the central nervous system following vaccinations is thoroughly analyzed. During November and December, 1922, there occurred amongst those recently vaccinated in and around London a few cases of an acute nervous disease of uncertain nature. Attention was first called to this in December, 1922, when four cases of the kind were admitted to the London Hospital, all of them fatal. In each instance there was a history of recent vaccination, and Dr. Turnbull, the Pathologist to the Hospital, was led to consider the cases as possibly associated with the vaccination on account of an apparently similar instance which had come under his observation in 1912. As a result of further inquiries a total of 11 cases, including the four above mentioned were brought to light in eight districts of the London area. These cases were, with one exception, primary vaccinations about the school age, and the period intervening between the onset of the illness and the vaccination ranged from 6 to 12 days. Seven of the cases were fatal, and the deaths were ascribed in 4 cases to polioencephalitis, in one case to acute anterior poliomyelitis and in 2 cases to meningitis. No similar cases were reported until the summer and autumn of 1923. During that period,

however, cases of acute nervous disease following vaccination were reported from various parts of the country, the onset of illness being usually 10 to 14 days after vaccination. These cases were widely spread, mainly in the southwest and midlands. For instance, there occurred at Tredegar what was thought to be a small outbreak of polioencephalitis affecting four children from 6 to 11 years of age. Three of them died; in these three the onset was 10 to 11 days after vaccination. In the fourth, which recovered, the interval was 12 days. At the time of these occurrences, smallpox was prevalent and vaccination largely increased in consequence. In London an unusually large number of persons were vaccinated. Similarly, in the summer of 1923, smallpox was again prevalent and a very large amount of vaccination and revaccination was going on. The cases of nervous disease coming to knowledge in this period were distributed to areas in some of which there had been a good deal of primary vaccination of children of school attendance age. Several other cases of nervous disease, fifteen in number were incidentally discovered during routine inspection duties by medical officers. Suspicion was aroused that the occurrences might be more widespread in distribution, and steps were therefore taken to ascertain whether similar cases were occurring generally throughout the country. The Registrar-General was asked to supply lists of deaths under 15 years of age from the following causes:— Poliomyelitis, Polioencephalitis, Encephalitis Lethargica and Meningitis, (Tuberculosis and other forms.) Inquiry was then made in respect to every case in the lists, thus obtained in regard to the performance of vaccination within one month of the onset of the fatal illness. The Registrar-General's returns showed that during the months of July and August, 1923, 601 deaths at this age period were reported as due to one or another of the above causes. In these were only 10 cases in which vaccination had been performed within a month of the onset of the illness, and an analysis of these cases showed that the probable diagnosis in 3 cases was post-basal meningitis, in 5 cases tuberculous meningitis, and in 2 cases the diagnosis was obscure. These figures did not bear out the idea that any considerable portion of the deaths registered during July and August, 1923, due to meningitis and other diseases of the nervous system were associated with recent vaccination. The cases of encephalitis occurred in two groups separated by an interval of some six months, and in each the incidence of the disease was mainly confirmed to a very limited period. The first group of 11 cases occurred in London and its environs, and the dates of onset of the disease ranged from November 14th to December 15th, 1922, the cases having been vaccinated in the last nine days of November. Four of this series were examined histologically by Dr. Turnbull. No other cases throughout England and Wales were reported at this time, but it was discovered later that on January 4, a case occurred at Colwall in Herefordshire. There were no further cases till the summer of 1923 when a second group arose consisting

of 50 cases. These occurred mainly in the provinces, most of them in the month of July. Of the 50 cases, one was vaccinated in May, 5 in June, 31 in July, 2 in August, 7 in September and 4 in October. Since the above, no other cases have been reported with the following exceptions: At Winsford, Cheshire, a man aged 45, who was vaccinated on February 9th, 1924, developed cerebral symptoms 13 days later, the condition being diagnosed as "Encephalitis lethargica"; and in Birmingham in April, 1925, an infant who was vaccinated on April 6th, developed convulsions on the 15th, lost consciousness and died, the diagnosis being "Convulsions, meningismus following vaccination". There was an almost six months interval between the first group of cases and the second, and over a year has elapsed since the last case. During these periods vaccination has continued more extensively than usual, since smallpox has been prevalent to a considerable extent and over a wide area. Up to the date of this report, therefore, there were 64 cases which form its basis, two of these having been reported as the report was in press and are not included in this summary. Of 62 cases, there were 40 females and about 22 males, with an average age of 10½ years. In 7 cases, the ages ranged from 20 to 50 years. The mortality was 36 out of 62, or rather over 58 per cent. No direct proportional relation between the cases of postvaccinal encephalitis and the number of persons vaccinated was found to exist. The practitioners' diagnoses of the nervous symptoms from which 62 cases suffered showed great variation. The greater number of the cases were attributed to: meningitis, polioencephalomyelitis and its varieties, and encephalitis lethargica. In the area in which the cases occurred there was a high incidence of endemic poliomyelitis and polioencephalitis. In these areas vaccination was also much above normal. As to the lymph used, rabbit stocks predominated largely over calf stocks, the latter in fact being very few. The clinical data at the disposal of the Committee were in the majority of cases very scanty. These data suggest that the majority of the cases (47 out of 62) were alike and represent a homogeneous group. In most instances, the onset of symptoms was rapid and the course of the disease acute. The predominant symptoms were of cerebral rather than of spinal origin, and included fever, backache, headache, vomiting, strabismus and varying degrees of clouding of consciousness. Where paralysis of the limbs occurred, it was generally of the upper motor-neuron type. In other words, these cases, presented the symptomatology of encephalitis, indicating a diffuse inflammation of the brain, without special localization, and with very little evidence of involvement of the cord. Nine of ten cases, in which the after histories were followed up, recovered completely, without the paralyses which follow ordinary poliomyelitis or the mental or other disturbances which form the common sequelae of polio-encephalitis and encephalitis lethargica. One of the cases developed hemiparesis, probably permanent. None of the cases showed any complication as regards the vaccination process. In all, the course of vaccination appears to have

been normal and to have given rise to no undue constitutional disturbance, to no excess of local inflammation and to no septic invasion. There is, therefore, no reason to suppose that any marked debility occurred owing to the vaccination which might have led to a lowering of resistance. Postmortem records are available in six cases of the series. In all there was some degree of meningeal congestion, usually slight, and in one case there were slight meningeal hemorrhages. A little meningeal thickening was noted in one case, with some edema, and minute nodules which proved on section not to be tuberculous in character. The brain itself was found congested, the blood vessels conspicuous; in most cases, hemorrhages were noted in the nervous tissue, chiefly about the blood vessels. Softening of the brain was absent. In the spinal cord, marked softening was noted in one case, and local blurring of the pattern of the gray and white matter in another. Otherwise the changes were similar to those seen in the brain, namely, congestion and punctiform hemorrhages. The changes in other viscera were slight. The histological appearances were those of a diffuse encephalomyelitis, or meningo-encephalomyelitis. The nervous tissues showed a small celled infiltration of perivascular distribution. The perivascular sheaths contained lymphocytes, with larger cells having a large clear nucleus, possibly endothelial in nature. Polymorphonuclear leucocytes and plasma cells were less common as a rule, but in certain cases were well defined. In the parenchymatous foci the predominant cells had a large, clear, somewhat irregular nucleus, and many were possibly derived from the neuroglia; lymphocytes were less abundant than in the perivascular sheaths. In these foci, which have an edematous appearance, chromatin fragments were also present, derived from cells which have broken down. Actual destruction of the neurones was rarely seen. As a rule the nerve cells still showed Nissl granules. Nevertheless, chromatolysis was often present, and on careful search more severely damaged neurones were found. Capillary hemorrhages occurred, but were infrequent and slight. Hyaline thrombi were not uncommon and were often associated with edema of the surrounding tissues. The data brought before the Committee suggest that the encephalomyelitis which followed vaccination in the cases under review was due to infection with a virus belonging to the group of neurotropic "filter passers." The essential problem is the relation between the cases of encephalitis under review and vaccination. Three possibilities suggest themselves. In the first place, it is possible that the cases of encephalitis were genuine sequelae of vaccination, and due solely to the virus of vaccinia. The second possibility is that the cases of encephalitis, though coincident with vaccination, were due to some different and independent cause. The third possibility is that the cases of encephalitis were due to the combined action of two morbid vira, viz., vaccinia and some other familiar or unfamiliar virus. In the majority report of the Committee, it is stated that there would appear to have been in the cases concerned something more than mere overlapping in time of vaccination

with some familiar or unfamiliar neurotropic virus, and that the unusual clinical and histological manifestations and lethal character of the best studied cases suggest that a combination of vira was operating. In the minority report made by Dr. McIntosh, he states that the histological and pathological appearances of the fatal cases are uniform and present an entirely new picture, and that he is strongly of the opinion "that we have had to deal with a hitherto undescribed inflammatory lesion of the central nervous system". He considers vaccination to have been a casual factor and not a mere coincidence, and that the infection was either introduced by vaccination or that vaccination made the central nervous system susceptible to it. From 1923 to 1927, 124 cases of postvaccinal encephalitis occurred in Holland. The incidence of the disease in Holland during 1927 and the first half of 1928 has been estimated at one case per 2,800 vaccinations. Public opinion in that country has been turned against compulsory vaccination. Towards the end of 1927, compulsory measures were suspended, and in 1928 there were only 52,683 vaccinations as against 173,672 in 1926 and 150,653 in 1927. This suspension will continue until the end of the present year. The fact that practically all the cases of encephalitis followed the use of rabbit lymph suggests the possibility of infection with "rabbit encephalitis", which is extremely common in American laboratory rabbits. The virus of this infection may be carried over in the lymph used for vaccination, and may possibly produce an encephalitis in susceptible children. Apropos of the use of rabbit lymph the following questions were put to the Minister of Health in the House of Commons in July: "When rabbits first began to be used in the production of government lymph supplies, whether any cases of post-vaccinal encephalitis were reported in this country prior to such introduction of rabbit lymph: Whether his medical advisors have considered the advisability of dispensing with the use of rabbits for the purpose in question: Whether he is prepared to guarantee that any child or person vaccinated with government lymph will not be seriously injured by the operation; and, if it is not possible, whether he will consider the desirability of introducing legislation to secure that compensation shall be given to the parents or dependents, as the case may be?" Until the question of etiology is settled the use of rabbit lymph should be stopped. Since Wilson and Ford have reported four cases of postvaccinal encephalitis in America, this disease becomes a matter of importance to us in this country, and steps towards its prevention should be taken by those concerned in vaccination. The unfortunate result of the situation is the ammunition afforded the anti-vaccinationists who have seized upon the occasion to further their cause against compulsory vaccination. It is, therefore, highly desirable that the problem of the etiology and prevention of postvaccinal encephalitis be investigated at once by intensive research. A quick solution of this question is necessary for many reasons, the most important of which is the prevention of an anti-vaccination stampede, which resulting great increase in the incidence of smallpox.

Abstracts

Attempted Production of Vaccinal Encephalitis in Rabbits with a Testicular Virus. By RICHARD THOMPSON (Proc. Soc. f. Exper. Biology and Medicine, 1929, XXVI, p. 559).

The reproduction of vaccinal encephalitis in rabbits is of interest at this time chiefly in view of the prevalence of postvaccinal encephalitis in some European countries. The possible use of the rabbit's brain as a medium for mass production of sterile vaccine (advocated by Levaditi) also adds importance to the question. A considerable number of European workers have succeeded in producing what they regard as a vaccinal encephalitis in rabbits. Levaditi and his coworkers since 1921 have developed a strain of vaccine virus known as neurovaccine which produces regularly on intracerebral injection into rabbits a typical encephalitis with paralytic symptoms and death in 4-7 days. They regard it as a virus adapted to the central nervous system by passage and consider that it has acquired neurotropic properties. They first adapted it to the brain by alternate brain and testicular passage, later omitting the testicular passages. Blanc and Caminopethos found that ordinary calf vaccine passed through the rabbit's cornea and then to the brain was sufficiently adapted to cause a fatal encephalitis. Herzberg produced a vaccinal encephalitis by the intracerebral injection of a virus adapted to the rabbit's testicle. The great majority of workers, however, have found no adaptation necessary and consider the encephalitogenic property as one inherent in ordinary vaccine virus. Marie, Krumbach, Condrea, Bachman and Bigliere, Burnet and Conseil, and Winkler have all succeeded in producing an encephalitis by the intracerebral injection of ordinary calf vaccine lymph purified by various means. Krumbach found no difference between calf lymph and lapine (vaccine adapted to rabbit's skin by passage). Condrea was unable to detect any difference between the action of cutaneous and testicular virus in the brain—both producing encephalitis. Bachman and Biglieri used four strains of vaccinia and one of variola and obtained identical symptoms with all, although the symptoms described by them differ markedly from the typical picture described by most other authors. They also found no difference between testicular and dermal virus. Burnet and Conseil found that chloral or opium injections increased the susceptibility of the brain. Ledingham states that ordinary vaccine virus requires no special adaptation to the brain to kill by intracerebral injection. Reports of failures to produce encephalitis by vaccine virus are comparatively rare. Calmette and Guerin injected virus intracerebrally from the fourth, but not the seventh day, but make no mention of any symptoms or fatal disease. Camus was unable to produce encephalitis in rabbits by the intracerebral injection of pure vaccine and on the basis of this and the difference between the skin lesions of ordinary vaccine and Levaditi's neurovaccine is inclined to regard Levaditi's product as a mixture of vaccine virus with some other unknown virus. Walthard could not produce encephalitis by the injection into one rabbit of virus deposited in the brain of another after corneal infection. There is no report in the American literature on the production of encephalitis by an ordinary strain of vaccine, either by direct injection or with any means of adaptation, although Levaditi's neurovaccine has been used by a number of workers. In view of this Thompson considered it worth while to endeavor to produce an encephalitis in rabbits by using a strain not known to be adapted to the brain. The virus used was the testicular strain adapted by Noguchi originally. Injection into the fourth ventricle was used

at first because of its simplicity and its very successful use with herpes encephalitis. Later only direct intracerebral injection was used. Testicles and brains for passage were ground up with sand and a twenty per cent suspension in saline made and centrifuged to remove coarse tissue particles. The presence of virus was tested for by intradermal injections. The strain of virus used when injected by either method did not produce in any animal a fatal encephalitis or even any symptoms which could not be ascribed to the mechanical effect of the injection. The virus was found to survive at least four days in the brain after intracerebral injection but only for twenty-four hours after ventricular injection; with ventricular injection and previous meningeal irritation by sterile broth attempts to adapt the virus to the brain by 24-hour brain to brain passage were negative. Virus present in the first passage brain had completely died out by the fourth passage and fourth passage did not revive it. Animals of the series allowed to live showed absolutely no symptoms. Brains of two animals, dying after ventricular injection, which contained same virus, produced no symptoms, when injected into other animals. With direct intracerebral injection attempts to adapt the virus by brain to brain passage at 7-day intervals were negative. Alternating brain and testicular passage, as used originally by Levaditi, was also without result. The virus could be kept alive apparently indefinitely by alternate brain to testicle transfer but no evidence of any acquirement of intracerebral pathogenicity could be detected and if the testicular passages were omitted the virus soon died out. In conclusion, the strain of virus used is definitely not encephalitogenic for rabbits; if it can be made to produce encephalitis it can do so only with extreme difficulty. In view of the apparent ease with which many European workers have succeeded in producing encephalitis with an ordinary strain of vaccine virus, and the lack of positive or negative reports of any such attempts in this country, this failure to obtain a vaccine encephalitis in rabbits is considered of interest. An explanation which offers itself is that the power to produce encephalitis depends upon the strain of virus, some strains producing it readily, some only after adaptation and some not at all. The theory of Camus that a virus which causes encephalitis is contaminated by some unknown virus must also be held in mind. (Note by Editor: This work of Thompson's is of great value apropos of the present excitement in Europe over post vaccinal encephalitis. The editor believes that the theory of Camus of a vaccine virus contaminated by a neurotropic virus is most probably the true explanation of the encephalitis-producing vaccine virus. As suggested in the editorial in this number, may this unknown neutropic virus not be the agent of spontaneous rabbit encephalitis, which carried over with rabbit lymph may produce encephalitis in susceptible human beings? Levaditi's experiments can be explained on the grounds of a coincident infection in the rabbits with encephalitis. The possibilities of a relationship between rabbit encephalitis and post vaccinal encephalitis constitute a problem for which there should be a speedy solution sought.)

Local Microscopic Changes Following the Administration of Antisyphilitic Drugs. By O. M. Gruhzit (Arch. of Derm. and Syphil., June, 1929, p. 922).

Gruhzit has studied the pathologic changes produced at the point of injection in animals of the main types of antisyhilitic drugs. From this study it appears that the administration of the arsphenamine type of drugs intramuscularly invariably results in the formation of sterile abscesses, the healing of which is slow. At the end of eight weeks the healing has shown little progress. In this respect, sulpharsphenamine causes just as extensive an injury as neoarsphenamine. The mercury compounds produce the same type of injury only in a lesser degree. The injured areas, however, are more rapidly absorbed and fibrosed, especially when mercury thiobenzoate, benzoate and cyanide are used. The ultimate result is a scar tissue at the site of injection. The bismuth compounds cause local injury according to the degree of corrosiveness. The least injury is produced in the case of water-soluble compounds, such as bismuth thioglyco-

late. The bismuth compounds suspended in oil or water cause considerable local necrosis, which is usually followed by the formation of a sterile abscess. The absorption of the necrotic material with the formation of a scar is a prolonged process. This, however, occurs more readily in the muscle under constant exertion than in an inactive muscle. Bismuth thioglycolate, a water soluble and tissue-soluble preparation, causes the least injury to the tissues at the site of injection and is followed by a most rapid healing of the lesion. The tissue-fluid insoluble bismuth preparations must first be dissolved by the tissue fluids before they can be absorbed. Phagocytic action, if present, appears to be of minor importance.

Prevention of Diabetic Deaths. Elliot P. Joslin (Massachusetts Dept. of Public Health, June, 1929).

In a pamphlet distributed by the Massachusetts Department of Public Health, Joslin has set forth the diabetes mortality in that state, and the principles for the prevention of diabetic coma. Diabetes under the age of 20 has almost disappeared from the state; between the ages of 20 and 40 the mortality from the disease is lower than at any other time in this century, whereas above the age of 50 there has been a gradual rise. This rise does not begin for men until the age of 60, so that it is the women after the age of 50 who are chiefly responsible for the increasing death rate in Massachusetts. The diabetic mortality can be lowered still more provided the physicians of the state attack coma more efficiently. Out of 1044 fatal cases of diabetes reported to the Metropolitan Life Insurance Company up to April 15, 1929, coma was responsible for 433 deaths or 41 per cent. It is really the fault of the profession, says Joslin, that the mortality from diabetes is not decreasing, because diabetic coma is always preventable and nearly always curable. As one of the best practitioners in the state said recently, "Diabetes is a chronic disease, but doctors do not realize that it has acute manifestations." Indeed coma develops because of ignorance, negligence or carelessness. Diabetics go into coma carelessly because they break their diets and overeat; they go into coma as a result of negligence when in the course of an infection, either general like measles or local like a boil, they neglect to make the proper tests to determine whether they are using enough insulin; they go into coma ignorantly, because they stop their insulin when they cease to eat for one cause or another. A diabetic should never omit his insulin unless his urine is sugar free. He must never forget that when he stops eating, he begins eating himself—his own body—and so still requires insulin, and often very much more insulin than before. If he has an infection as a cause of his loss of appetite he should know that an infection lowers the value of insulin and thus makes more insulin than usual a necessity. Coma, and by diabetic coma, is meant acid poisoning, may steal away a diabetic before he or his friends suspect it. Within a few hours such mild symptoms as indigestion, lack of appetite, and pain in the abdomen may be followed by difficult breathing, drowsiness and unconsciousness. The only safe way for the diabetic to protect himself against coma is to keep well and sugar free all the time. Joslin tries to instill the following principles into the minds of every diabetic he sees: Whenever he feels ill and sick he should call his doctor, go to bed, take a hot drink every hour, take an enema, keep warm, get a nurse or someone to care for him. Another good rule is to have boiled water ready for the doctor when he arrives in case he wishes to use it. Promptness in diagnosis of coma is everything, and next to it comes energetic treatment at the earliest possible moment. If coma exists the doctor must give up everything else until the patient comes out of it. Insulin is usually required every half hour in 10-40 unit doses or more, varying with the severity of the symptoms, and if it is given intravenously it should always be given subcutaneously at the same time. Dehydration of the patient must be overcome by the subcutaneous injection of normal salt solution and one cannot rely on fluids given by the mouth or rectum. The heart is almost always weak and needs stimulation with caffein sodiobenzoate, 7½ grains, and this may be given every hour if need be, for three or four doses. On

account of the weakness of the heart, salt solution must be injected very slowly if given intravenously. With children and usually with adults the stomach is distended and unless evacuated prevents the retention of liquids, such as water, gruels, ginger ale, or the juice of 2-3 oranges, in other words, carbohydrate amounting to 50 grams. Therefore, the stomach should be gently washed out.

Thrombo-Angiitis Obliterans. Experimental Reproduction of Lesions. LEO BUERGER (Arch. of Path., 1929, p. 381).

In a paper published in 1914 Buerger expressed his conviction that the acutely inflamed veins and nodosities of thrombo-angiitis obliterans could furnish the material in which an infectious agent-virus or micro-organism might reside and be brought to light; second, that these foci might be utilized for the reproduction of the acute lesions of the malady. He has carried out investigations extending over ten or more years in the attempt to find a micro-organism. Failing in this effort he turned his attention to the reproduction of the acute lesions of the disease. He employed simple ligation of the veins of the fore-arm or arm for control purposes; he implanted or inoculated the coagulum of acute thrombo-angiitis obliterans into the lumen of ligated veins, and implanted acute thrombo-angiitis coagulum against the walls of ligated veins in man and monkeys. As a result, the paravascular implantation of clot from cases of thrombo-angiitis obliterans was followed by the development of typical lesions of the disease in the apparently healthy ligated veins of the inoculated person. In two experiments on monkeys he failed to produce other than a bland thrombosis, a fact which would suggest that these animals may be immune. Other types of monkeys will be employed as soon as material becomes available.

Studies of Experimental Streptococcus Arthritis. IV. Effect of Sodium Salicylate on Skin Allergy. R. A. KINSELLA and O. E. HAGEBUSH (Proc. Soc. f. Exper. Biology and Medicine, 1929, XXVI, p. 857).

The effect of sodium salicylate on the development of dermal allergy in the presence of hemolytic streptococcal arthritis was studied because this drug is commonly employed in the treatment of acute rheumatic fever, and because the studies of Swift concerning the pathogenesis of this disease support the idea that allergy to streptococcus of various kinds is a factor in its production. As previously reported by these workers, the production of arthritis in rabbits by the inoculation into a knee joint of 0.1 cc. of 24 hr. broth culture of hemolytic streptococcus will be followed in 6 days by the appearance of a strongly positive local reaction to intradermal injection of a filtrate of a 5 days' culture in Harley's medium. The skin reaction takes 12 to 24 hours to develop. All rabbits were tested previous to the experiment and found to give no such reaction. Twenty-four rabbits were employed for this study, twelve of which received sodium salicylate, 6 received the drug for a considerable period before receiving an intra-articular injection of 0.1 cc. of culture of hemolytic streptococcus, and 6 rabbits received the drug and the culture at the same time. The dose of sodium salicylate was 0.2 gm. per kilo in 4 percent solution and was given intravenously. The first series of 6 received 8 daily injections of salicylate and after an interval of 12 days, during which the animals were in good health, received 6 more injections given at 2 day intervals. After the injection of streptococci into the knee joint, 3 more daily injections of sodium salicylate were used, and 3 days later skin tests were made. At this time 3 of the series were dead. The 3 survivors showed completely negative tests. In the second series of rabbits the animals received the injection of salicylate 24 hours before the intra-articular injection was made. Thereafter 4 daily injections of salicylate were given and 4 animals survived. These gave completely negative tests. In the 12 control rabbits strongly positive skin reactions occurred 6 days after arthritis was produced and the reactions remained positive. The arthritis was highly fatal to all the animals but more so to those receiving the salicylate. The conclusion is supported, that the intravenous injection of sodium salicylate prevents the development in rabbits having a streptococcal arthritis, of a positive skin reaction to filtrate of hemolytic streptococcus culture.

Reviews

Principles and Practice of Electrocardiology. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. 226 pages, 61 illustrations. The C. V. Mosby Company, St. Louis, Mo., 1929. Price in cloth, $7.50.

The use of the Einthoven string galvanometer by a privileged few has so thoroughly demonstrated its value in the diagnosis of heart diseases that a more general demand for electrocardiographic apparatus has been created. This increasing demand has enabled manufacturers of scientific apparatus to develop and market commercial models easy to operate and free from the inconveniences originally attached to the use of such apparatus. But unfortunately the training of medical men in the use of such apparatus and in the interpretation of electrocardiograms has not kept pace with this demand. Few courses in electrocardiography are included in under graduate or post graduate curricula of medical schools, so that opportunity for systematic instruction is decidedly restricted. It is obvious, therefore, that a more general self-training of physicians in the principles and practice of electrocardiography must take place. The need of a simple yet comprehensive treatise by an author who can reasonably lay claim to experience, both in the use of such apparatus as well as in the didactic presentation of this particular subject, is therefore apparent. This book is written with the object of filling this need. It is based on the author's practical experience in giving courses in electrocardiography in the medical schools of Cornell University and of Western Reserve University. The book is divided into three sections. The first deals with the general principles and procedures of electrocardiography, with the physics of the galvanometer and accessory systems, and on the basis of such knowledge, passes on to a consideration of the operation of different models. The second part explains the cause of the normal electrocardiographic deflections and their relation to physical and physiologic processes in the heart. It then proceeds logically to an analysis of abnormal cardiac disturbances and their effects on electrocardiograms. The third section considers a series of abnormal electrocardiograms from patients which are presented as unknowns. It points out the evidences of abnormalities in each, discusses their significance in terms of clinical physiology, and thus arrives at a diagnosis. This is followed by a brief discussion of the salient features of the disorder studied, and of the treatment which has been given the stamp of approval. Experience has shown that in this way all the more common abnormalities can be presented in an interesting fashion and a method for the scientific evaluation of other records is taught. This is a very complete survey of the subject, and an indispensable book for the internist. It is well written in a clear concise style, and sufficiently illustrated. It is an important addition to the literature of electrocardiology.

Clinical Laboratory Methods. By RUSSELL LANDRAM HADEN, M.A., M.D., Professor of Experimental Medicine, University of Kansas, School of Medicine, Kansas City, Kansas. Third Edition. 317 pages, 69 illustrations and 4 color plates. The C. V. Mosby Company, St. Louis, Mo., 1929. Price in cloth, $5.00.

This manual was written originally to provide a simple yet complete outline for the average clinical laboratory worker. Only such methods were described as had proved both practical and dependable. Certain procedures which are seldom used, such as the qualitative determination of acetone bodies in the urine, have been omitted. Other methods have been revised. The one most im-

portant addition is the technic for the Kahn precipitation test for syphilis. A few entirely new methods, such as the determination of indican in blood, have been added. A survey of this edition lends us to note many important omissions. For instance, the only method for the staining of spirochaeta pallida given is one employing Wright's blood stain, a method which does not compare with the silver nitrate cover-glass methods. Methods are given for the staining of connective-tissue fibers, tubercle bacilli in tissue and Gram-positive bacteria in tissue, but no method is given for the staining of spirochaeta pallida in tissues. Surely the demonstration of spirochetes of syphilis in tissue sections is among the most important, but most neglected, functions of the clinical laboratory, and a book on clinical laboratory methods which omits these cannot be said to be complete. Further, the laboratory diagnosis of Tularemia and Malta Fever is not even mentioned. This book cannot be considered as up to date.

Textbook of Clinical Neurology. For Students and Practitioners. By M. NEUSTAEDTER, M.D., Ph.d., Visiting Neurologist, Central Neurological Hospital, Welfare Island; Clinical Professor in Neurology, New York Polyclinic Medical School and Hospital, Outpatient Department. Stuyvesant Polyclinic, St. Mark's Hospital, Neurologist King's County and City Hospital, Welfare Island, New York. With an Introduction by EDWARD D. FISHER, M.D., Professor Emeritus of Neurology, University and Bellevure Hospital Medical College, New York. 602 pages, 228 illustrations, same in colors. F. A. Davis Company, Philadelphia, 1929. Price in cloth, $6.00.

This book is written primarily for the medical student and general practitioner rather than for the neurologist. In writing it, therefore, it has seemed wise to depart from the classical arrangement and to present the material according to its actual occurrence in medical practice. The general practitioner or the student at the patient's bedside hears a story and sees symptoms. Not being a specialist in the field of neurology, he is not likely to recognize whether the symptoms found relate to disturbance of the brain, cord, peripheral nerves, muscles or endocrine glands. Consequently the first thing looked for, in consulting a reference book, is symptomatology, and in the usual textbook the arrangement of the book forces him to search from chapter to chapter. In order to save time the student and general practitioner require a working knowledge of the subject of neurology in as concise, lucid and complete a manner as possible. The author has been frequently importuned by his students to write a book of this type, a sort of *vade mecum*. This book is the result. Its principal theme is the semiology of the disorders of the nervous system. Symptom complexes found at the bedside or in the consultation room, constitute the chapter divisions. Under these are discussed the various diseases exhibiting such syndromes and their relationship to the structures affected—nervous, endocrine, muscular or osseous, as the case may be. Thus, the description of diseases begins with symptoms, and after the symptoms have been fully described, etiology and pathology, diagnosis, prognosis and treatment are taken up in the order named. It should be emphasized that the material of this volume is based mainly upon the author's personal clinical and pathological experience during the last twelve years. He has made a special effort to be brief and lucid, yet to incorporate all the material facts without befogging the issue. In this he has been unusually successful. Especial attention has been given to the subject of polioencephalitis and epidemic encephalitis. The tremograms devised by the author also constitute a novel feature of the book. The illustrations are abundant and for the greater part very good. Altogether this book is to be recommended as a valuable adjunct in the study of neurology.

The Common Head Cold and Its Complications. By WALTER A. WELLS, A.M., M.D., F.A.C.S., Professor of Oto-Laryngology, Georgetown University, Washington, D.C. With an introduction by HUGH S. CUMMINGS, M.D., Surgeon General, United States Public Health Service. 225 pages, 15 illustrations. The Macmillan Company, New York, 1925. Price in cloth, $2.75.

According to a survey made by the Public Health Service, there is, on account of colds in the United States, an average annual loss of work of about two and one-fifth days for each worker, so that taking into consideration only that part of our population engaged in industry, which is about forty-two million, there may be estimated a loss of more than ninety million work days per year. Rendered in terms of money this means a loss of not less than four hundred and fifty million dollars every year on account of colds alone. This, however, by no means represents the total economical loss of colds, for it does not take into consideration the loss in energy and efficiency for many days following an attack, the loss from illness indirectly due to colds, or the cost of medicine and medical and nursing services. There can be no doubt that the unrestricted occurrence of the common head cold seriously affects the health, happiness and efficiency of the human race. Are colds contagious? Are drafts harmless? Do vaccines prevent? Is the use of spray and gargles advisable? Ought adenoids and tonsils to be removed? Is sinus inflammation curable? These are some of the vital, pressing questions, upon which enlightenment is demanded and urgently needed. The aim of this book has been to answer these questions, and to explain to what extent colds are dependent upon general health as well as local conditions. Included is a special discussion of the subjects of diet, clothing, exercise, bathing and ventilation, which have a direct bearing upon the tendency to catch colds or the capacity to withstand them. The author believes that much can be done by judicious treatment of colds, which will not only tend to lessen the duration of the cold but to modify its course, to prevent complications and to forestall unfortunate consequences. There is included in the book a chapter dealing with home care and the general principles of home treatment, indicating these general measures to be followed, and these which are contrary to sound doctrine and therefore to be avoided, with instructions as to what the patient may safely do for himself and under what circumstances he should consult a physician to insure recovery. The complications of colds are considered in chapters on Adenoids and Tonsils, Sinus Disease and Voice Trouble. The author hopes that a rational up-to-date presentation of these topics may not be without value in dissipating some of the superstitious opinions and absurd practices that have ever clung to the subject of colds, which he believes is largely due to the indifference of the medical profession itself and its failure to instruct the general public in a matter of such great importance to health and happiness. Much useful information is contained in this little book.

Handbook of Microscopical Technique. For Workers in Both Animal and Plant Tissues. Edited by C. E. McClung, Ph.D., Professor of Zoology and Director, Zoological Laboratory, University of Pennsylvania. 495 pages, 43 illustrations. Paul B. Hoeber, Inc., New York, 1929. Price in cloth, $8.00.

The book is divided into two parts. Part I outlines approved methods for the inexperienced worker and Part II for the experienced investigator. By a system of cross-reference between the two parts, all unnecessary repetitions are avoided. In Chapter I general methods are considered; in Chapter II methods for fresh material; in Chapter III bacteriological methods; in Chapter IV general botanical microtechnique; in Chapter V cytological methods; in Chapter VI embryological methods; in Chapter VII histological methods; in Chapter VIII protozoological methods; in Chapter IX fixation and fixatives are discussed; in X stains and staining; while Chapter XI is given up to a miscellaneous consideration. On careful examination this book proves to be a great disappointment. Instead of taking the place of the German Encyclopedia of Microscopic Technique, at least as far as the worker in pathology is concerned, the parts of this book that can be utilized by the practical pathologist are very slight indeed. No methods for the staining of spirochetes are given, and the special methods for the demonstration of hemosiderin, calcification, etc., are not included. The book is written from the standpoint of general science rather than from that of a practical pathological lab-

oratory. For this reason it will be of little use to the pathologist, with exception of the neuropathologist, since neurological technique is more adequately presented. The same is true of botanical and general zoological technique.

The History of Hemostasis. By SAMUEL CLARK HARVEY, M.D., Professor of Surgery, Yale University, Surgeon in Chief, New Haven Hospital. 128 pages, 19 illustrations. Paul B. Hoeber, Inc., New York, 1929. Price in cloth, $1.50.

Another of the delightful little volumes on medical history from the house of Hoeber! Reprinted with additions and corrections from Annals of Medical History, N. S. Vol. 1, No. 2, March, 1929. In this *obiter opus* in medical history, the control of hemorrhage has been chosen as the thread to be followed amidst the varying fortunes of surgery. Beginning with the mention of the superstitious respect for blood held by primitive man and the attempts at hemostasis in the epics of early Greece and Rome, the beginning of hemostasis in the early Medicine of Egypt, China, India, Assyro-Babylonia, and Greece are described. The doctrine of the pneuma befogged the observations of the early anatomists. In the Golden Age of Roman medicine, from Celsus to Galen, the theory of pneuma was dispersed, the knowledge of anatomy was furthered, and hemostasis progressed to the use of ligatures and styptics. The next step in hemostatic usage was the almost universal employment of the cautery, which lasted up to the time of Paré, who in 1564 advised the abandonment of the cautery and adopted the use of the ligature. In 1674, Morel was as far as can be determined, the first to use the tourniquet. This became the standard practice of the 18th century. Lister's part in the antiseptic ligation of vessels, the use of carbolized catgut, the application of an artery forceps and the casting about the vessel of a ligature, bring the manipulations of hemostasis up to the practice of the present day. "The groping Alexandrian anatomist, the practical Greco-Roman surgeon, the consumate Paré, the obscure Morel, and the patient experimentalist, Lister, contributed the essentials, a host of surgeons provided the refinements." As a result, the operator of today may delegate to the background of the procedure that which for ages was an almost insurmountable obstacle, and proceed without fear of hemorrhage calmly and unhurriedly, in such a manner as to ensure for the patient all that surgeons still can provide.

College News Notes

Dr. Walter S. Leathers (Fellow), Nashville, Dean and Professor of Preventive Medicine and Public Health, Vanderbilt University School of Medicine, has been appointed a member of the National Board of Medical Examiners to fill the vacancy made by the retirement of Admiral Edward R. Stitt (Fellow), U. S. Navy, as Surgeon General.

Dr. T. Homer Coffen (Fellow), Portland, Oregon, addressed the Portland City and County Medical Society, June 5, on "Misuses of Digitalis."

Dr. Frank R. Menne (Fellow), Portland, Oregon, addressed the Marion-Polk-Yamhill County Medical Society at Salem, June 4 on "Carcinoma of the Lungs."

Dr. Christopher G. Parnall (Fellow), Medical Director of the Rochester General Hospital, Rochester, N. Y., was installed as President of the American Hospital Association at the recent annual meeting in Atlantic City, N. J.

Dr. Henry Green (Associate), Dothan, Ala., was elected President of the Chattahoochee Medical and Surgical Association at its twenty-ninth annual meeting on July 10. Dr. Green is a past President of the Houston County Medical Society and of the Medical Association of the State of Alabama.

Dr. Hugh S. Cumming (Fellow), Surgeon General, U. S. Public Health Service, has been appointed by President Hoover to act on a planning committee to inaugurate a national investigation of the progress and present situation in the health and protection of childhood.

The Florida East Coast Medical Association was addressed on June 14-15 by Dr. Stewart R. Roberts (Fellow), Atlanta, Ga., on "Jaundice."

The honorary degree of Doctor of Science was awarded to Dr. James Allen Jackson (Fellow), Danville, Pa., during the recent commencement of Bucknell University.

Dr. Joseph McFarland (Fellow), Professor of Pathology, University of Pennsylvania School of Medicine, will become head of the new Cancer and Abnormal Growth Registry to be established in September at the Research Institute of the Lankenau Hospital, Philadelphia.

Dr. James B. Herrick (Fellow), Chicago, emeritus professor of medicine, Rush Medical College, gave the commencement address at Lewis Institute recently.

At the annual election of officers of the Chicago Medical Society, Dr. James H. Hutton (Associate), Secretary of the Society, was made President-Elect while Dr. Nathan S. Davis, III (Fellow) was elected the new Secretary.

During the seventh annual assembly of the Twin Lakes District Medical Society at Rockwell City, Iowa, Dr. Walter C. Alvarez (Fellow), Associate Professor of Medicine, University of Minnesota Graduate School of Medicine, spoke on "Diagnosis of Gastro-Intestinal Disease"; Dr. Julius H. Hess (Fellow), Professor of Pediatrics, University of Illinois College of Medicine, Chicago, spoke on "Diagnostic and Therapeutic Suggestions Covering Some Chronic Abdominal Conditions in Infants and Children", and Dr. William W. Duke (Fellow), Kansas City, Mo., spoke on

"Allergy as It is Encountered by the General Practitioner."

The program of the fifty-first annual meeting of the Medical Association of Montana included addresses by the following Fellows of the College: Dr. Frederic W. Schlutz, University of Minnesota Medical School, on "Fundamental Factors Underlying the Development of Alimentary Disorders in Infancy and Childhood"; Dr. Harold W. Gregg, Butte, on' 'Epidemic Meningitis", and Dr. Louis H. Fligman, Helena, Canti Cancer Film.

Dr. Solomon Solis-Cohen (Fellow), Philadelphia, will be the Chief of Staff of the new Willow Crest Institution for Convalescents at Willow Grove, Pa.

Dr. Milton M. Portis (Fellow), Chicago, has been elected Clinical Professor of Medicine at Loyola University School of Medicine.

Dr. Virgil E. Simpson (Fellow), Louisville, recently addressed the Tenth District Medical Society at Winchester, Ky., on "Differential Diagnosis of Tumor of the Lung."

Dr. David P. Barr (Fellow), Professor of Medicine, Washington University School of Medicine, St. Louis, who delivered the commencement address at Central College, was awarded the honorary degree of Doctor of Laws, on June 5.

Dr. Everett K. Geer (Fellow), St. Paul, was one of the speakers, on June 15, at an afternoon meeting of the Southern Minnesota Medical Association on the Mississippi River near Winona.

Dr. Alfred Stengel (Master), Philadelphia, addressed the annual meeting of the medical alumni of the University of Pennsylvania on June 15.

Dr. Thomas F. Abercombie (Fellow), Macon, Georgia, State Health Commissioner, was granted the honorary degree of Doctor of Public Health at the recent commencement of the University of Georgia.

Surgeon General Hugh S. Cumming (Fellow), Washington, D. C., was recently elected to honorary membership in the Delta Omega public health fraternity.

Dr. James L. McCartney (Fellow), Hartford, Conn., has been appointed chief of the department of mental hygiene of the Connecticut State Department of Health.

Dr. William A. White (Fellow), Washington, D. C., Superintendent of St. Elizabeth's Hospital, is Chairman of the Board of Managers of the Washington Institute for Mental Hygiene, which was incorporated on June 24. The Washington Institute for Mental Hygiene will open its first clinic in October.

Dr. Benjamin Goldberg (Fellow), Chicago, Secretary of the Board of Directors of the Municipal Tuberculosis Sanitarium, delivered the twentieth anniversary address at the Preventorium (Farmingdale), May 31, on the fundamentals of a national child health program.

Dr. Elliott P. Joslin (Fellow), Boston, was one of the speakers at the annual meeting of the Lake Keuka Medical and Surgical Association.

Dr. Lewis B. McBrayer (Fellow), Southern Pines, addressed the Third District Medical Society of North Carolina on "Organized Medicine".

Dr. Leroy H. Sloan (Fellow), Chicago, with the assistance of local physicians, held a Clinic at the Allen Memorial Hospital (Waterloo) on June 2nd, and in the evening addressed about seventy-five physicians from nearby towns.

Dr. Walter J. Wilson (Fellow), Detroit, on May 16 addressed the Lenawee County Medical Society, on diagnosis of heart disease with special reference to the electrocardiograph.

Dr. Edward D. Spalding (Fellow), Detroit, delivered an address before the Mecosta County Medical Society (Big Rapids) on "Modern Cardiac Therapy".

Dr. Samuel F. Haines (Associate), Rochester, Minn., was one of the speakers at the thirty-second annual meeting of the Upper Peninsula Medical Society held at Ironwood (Michigan), August 7-8; his subject was "Early Diagnosis of Exophthalmic Goiter".

Dr. David C. Wilson (Fellow), formerly of the staff of the Clifton Springs Sanatorium, has been appointed Associate Professor of Psychiatry and Neurology of the University of Virginia Department of Medicine (Charlottesville).

Dr. Peter Irving (Associate), New York, New York, has been appointed Assistant Secretary of the Medical Society of the State of New York.

Dr. L. R. Sante (Fellow), St. Louis, Missouri, is Professor and Director of the Department of Radiology, at the St. Louis University School of Medicine.

Dr. Harold Swanberg (Fellow), Quincy, Illinois, is Editor of "The Radiological Review".

Dr. Judson Daland (Fellow), Professor of Medicine, University of Pennsylvania Graduate School of Medicine, has been assisting in the campaign against the tsetse fly in Africa during the past few months.

Dr. W. McKim Marriott (Fellow), Dean and Professor of Pediatrics, Washington University School of Medicine, St. Louis, Presented a symposium on "Nutrition" during the twenty-eighth annual meeting of the American Society of Orthodontists, Estes Park, July 15-20.

Dr. Kenneth M. Lynch (Fellow), Charleston, S. C., was made President-Elect of the American Society of Clinical Pathologists, during its recent meeting at Portland, Oregon.

Dr. Stuart Pritchard (Fellow), Battle Creek, addressed the joint meeting of the Fulton County Medical Society of Ohio and the Lenawee County Medical Society of Michigan, on "Early Diagnosis of Pulmonary Tuberculosis."

Dr. James M. Anders (Master), Philadelphia, received the Degree of Doctor of Laws from Pennsylvania Military College, Chester, during its June graduation-day program.

Dr. Edward L. Bortz (Fellow), Philadelphia, is author of an article, "Visceroptosis," which appeared in the Journal of the American Medical Association, July 6, 1929.

Dr. Henry A. Christian (Fellow), Boston, is the author of an article, "Nephrosis"; a Critique, wihch appeared in the July 6th Number of the Journal of the American Medical Association.

Dr. Walter M. Simpson (Fellow), Dayton, Ohio, was awarded the Ward Burdick Research Award (gold medal) at the recent meeting of the American Society of Clinical Pathologists, at Portland, Oregon, for his researches in tularemia and undulant fever. At the meeting of the American Medical Association at Minneapolis last year, Dr. Simpson was awarded a gold medal for his exhibit of the pathology of tularemia.

Dr. A. S. Warthin (Master), has returned from England where he presented his work on syphilis before the British Medical Association at the Manchester meeting in July.

In the 1928 Atlanta Proceedings of the Inter-State Postgraduate Assembly of North America there is published a survey of Dr. Warthin's work on Cardiovascular Syphilis.